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LE11 5RH (GB). **WILLIS, Paul** [GB/GB]; AstraZeneca
R & D Charnwood, Bakewell Road, Loughborough Le-
icestershire LE11 5RH (GB).

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(74) **Agent: ASTRAZENECA**; Global Intellectual Property,
S-151 85 Södertälje (SE).

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(71) **Applicant** (*for all designated States except US*): **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) **Inventors; and**

(75) **Inventors/Applicants** (*for US only*): **EVANS, Richard** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough Leicestershire LE11 5RH (GB). **EYSSADE, Christine** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough Leicestershire LE11 5RH (GB). **FORD, Rhonan** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough Leicestershire LE11 5RH (GB). **MARTIN, Barrie** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough Leicestershire LE11 5RH (GB). **THOMPSON, Toby** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough Leicestershire

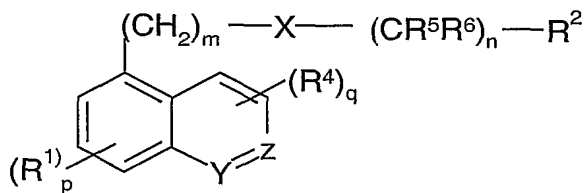
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(54) **Title:** NEW P2X7 RECEPTOR ANTAGONISTS AND THEIR USE



(IA)

(57) **Abstract:** The invention provides compounds of formula (IA), processes for their preparation, pharmaceutical compositions containing them, and their use in therapy. [Chemical formula should be inserted here. Please see paper copy] (IA)



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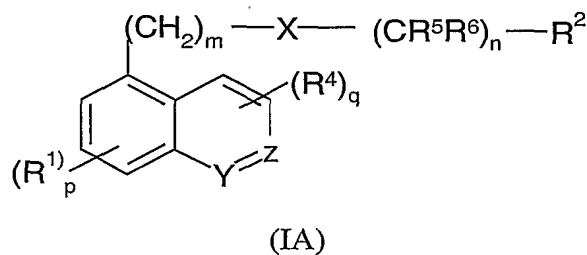
New P2X₇ receptor antagonists and their use

The present invention relates to certain heteroaryl amide derivatives, processes for their preparation, pharmaceutical compositions containing them, and their use in therapy.

The P2X₇ receptor (previously known as P2Z receptor), which is a ligand-gated ion channel, is present on a variety of cell types, largely those known to be involved in the inflammatory/immune process, specifically, macrophages, mast cells and lymphocytes (T and B). Activation of the P2X₇ receptor by extracellular nucleotides, in particular adenosine triphosphate, leads to the release of interleukin-1 β (IL-1 β) and giant cell formation (macrophages/microglial cells), degranulation (mast cells) and proliferation (T cells), apoptosis and L-selectin shedding (lymphocytes). P2X₇ receptors are also located on antigen-presenting cells (APC), keratinocytes, salivary acinar cells (parotid cells), hepatocytes and mesangial cells.

It would be desirable to make compounds effective as P2X₇ receptor antagonists for use in the treatment of inflammatory, immune or cardiovascular diseases, in the aetiologies of which the P2X₇ receptor may play a role.

The present invention provides a compound of formula (IA)



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein

p is 0, 1 or 2;

each R¹ independently represents halogen or C₁₋₆ alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C₁₋₆ alkoxy;

q is 0, 1 or 2;

each R^4 independently represents halogen or C_{1-6} alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C_{1-6} alkoxy;

m is 0, 1, 2 or 3;

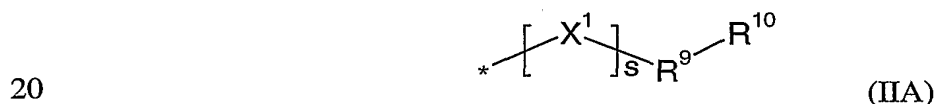
5 X is $-C(O)NH-$ or $-NHC(O)-$;

n is 0, 1, 2 or 3;

10 within each grouping CR^5R^6 , R^5 and R^6 each independently represent hydrogen, C_{1-6} alkyl or R^5 and R^6 together with the carbon atom to which they are both attached can form a 3- to 6- membered cycloalkyl ring;

R^2 represents a 4- to 9-membered cycloalkyl ring system, which cycloalkyl ring system can be optionally substituted by at least one substituent independently selected from halogen, hydroxyl, $-S(O)_f C_{1-6}$ alkyl, $-NR^7R^8$, $-C(O)OR^{12}$, $-OC(O)R^{13}$, $-C(O)NR^{14}R^{15}$, $-SO_2NR^{16}$
 15 R^{17} , $-NR^{18}SO_2R^{19}$, C_{1-6} alkoxy, C_{1-6} hydroxyalkyl or a C_{1-6} alkyl group which C_{1-6} alkyl group can be optionally substituted by at least one halogen; f is 0, 1 or 2;

one of Y or Z is nitrogen and the other is a group CR^3 wherein R^3 is a group of formula (IIA)



wherein X^1 represents an oxygen or sulphur atom, or a group $>N-R^{11}$ wherein R^{11} is hydrogen or a C_{1-5} alkyl group which can be optionally substituted by one or more substituents selected from hydroxy, halogen or C_{1-6} alkoxy; s is 0 or 1;

25 R^9 represents a bond or a C_{1-5} alkylene group, which can be optionally substituted by at least one substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy;

R^{10} represents hydrogen, hydroxyl, carboxyl, $-C(O)OR^{20}$, $-NR^{21}R^{22}$, $-C(O)NOH$, or a group $-WR^{23}$;

or R^{10} represents a 4- to 9-membered carbocyclic or heterocyclic ring, either of which may include bridging groups, which carbocyclic and heterocyclic ring can be optionally substituted by at least one substituent selected from halogen, hydroxyl, =O, carboxyl, cyano, C_1 - C_6 alkyl, C_1 - C_6 hydroxyalkyl, a group $-W'R^{24}$, $-C(O)NOH$, $-(CH_2)_tNR^{25}R^{26}$,
 5 $-(CH_2)_tC(O)NR^{27}R^{28}$, $-(CH_2)_tR^{29}$ $-(CH_2)_tNR^{30}C(O)R^{31}$, $-S(O)_rR^{32}$, $NR^{33}SO_2R^{34}$,
 $NR^{35}C(O)NR^{36}S(O)_rR^{37}$, $-S(O)_r(CH_2)_tNR^{38}R^{39}$, $-NR^{40}S(O)_rNR^{41}R^{42}$, $-S(O)_r$
 $(CH_2)_tC(O)OR^{43}$, or $-M(CH_2)_tC(O)OR^{44}$ wherein M represents a bond, O, or a group
 $>NR^{45}$;

10 t is 0, 1, 2, 3, 4, 5 or 6;
 r is 0, 1 or 2;

R^{21} and R^{22} are independently selected from hydrogen, C_{2-7} alkenyl, C_{1-6} alkylcarbonyl,
 $-SO_2R^{46}$, $-C(O)NHSO_2R^{47}$, a 3- to 8-membered carbocyclic or heterocyclic ring which
 15 carbocyclic or heterocyclic ring can be optionally substituted by at least one substituent
 selected from halogen, hydroxyl and carboxyl,
 or R^{21} and R^{22} may independently represent a C_{1-7} alkyl group which C_{1-7} alkyl group can
 be optionally substituted by at least one substituent independently selected from halogen,
 carboxyl, hydroxyl, $-NH(CH_2)_{2-4}OH$, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxycarbonyl, -
 20 $NR^{48}R^{49}$, $-C(O)NR^{50}R^{51}$, $-NR^{52}COR^{53}$, $-NR^{54}SO_2R^{55}$ and $-NR^{67}C(O)NR^{68}SO_2R^{56}$;

W and W' independently represent a bond, O, $S(O)_p$, $-NR^{57}C(O)-$, $-C(O)NR^{58}-$, $-SO_2NR^{59}$,
 $-NR^{60}SO_2-$, $>NR^{61}$, C_{1-6} alkylene, or a group $-O(CH_2)_{1-6}-$, $-S(O)_p(CH_2)_{1-6}-$, $-NR^{62}(CH_2)_{1-6}-$,
 $-(CH_2)_{1-3}O(CH_2)_{1-3}-$, $-(CH_2)_{1-3}S(O)_p(CH_2)_{1-3}-$, $-(CH_2)_{1-3}NR^{63}(CH_2)_{1-3}-$, $-(CH_2)_{1-3}$
 25 $NR^{64}C(O)(CH_2)_{0-3}-$, $-(CH_2)_{1-3}C(O)NR^{65}(CH_2)_{0-3}-$, or $-S(O)_p(CH_2)_{1-6}NR^{66}-$; p is 0, 1 or 2;

R^{23} and R^{24} independently represent a 3- to 10-membered carbocyclic or heterocyclic ring
 comprising from 1 to 5 heteroatoms independently selected from nitrogen, oxygen and
 sulphur, which carbocyclic or heterocyclic ring can be optionally substituted with at least
 30 one substituent selected from hydroxyl, =O, =S, nitro, cyano, amino, halogen, $-SO_2C_{1-6}$
 alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylamino, di- C_{1-6} alkylamino, and a

C₁₋₆ alkyl group which C₁₋₆ alkyl group can be optionally substituted by at least one substituent selected from halogen and hydroxyl;

5 R⁷, R⁸, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸ and R¹⁹ each independently represent a hydrogen atom or C₁₋₆ alkyl group optionally substituted by at least one substituent selected from hydroxyl, halogen and C₁₋₆ alkoxy, or any of R⁷ and R⁸, R¹⁴ and R¹⁵, R¹⁶ and R¹⁷ together with the nitrogen atom to which they are both attached can form a 3- to 8-membered saturated heterocyclic ring;

10 R²⁰, R³⁴, R³⁷, R⁴⁶, R⁴⁷, R⁵⁴, R⁵⁵, R⁵⁶, R⁵⁷, R⁵⁸, R⁵⁹, R⁶⁰, R⁶¹, R⁶², R⁶³, R⁶⁴, R⁶⁵, R⁶⁶, R⁶⁷ and R⁶⁸ each independently represent hydrogen or a C₁₋₆ alkyl group which can be optionally substituted by at least one substituent selected from halogen and hydroxyl;

15 R²⁵, R²⁶, R²⁷, R²⁸, R³⁰, R³¹, R³², R³³, R³⁵, R³⁶, R³⁸, R³⁹, R⁴⁰, R⁴¹, R⁴², R⁴³, R⁴⁴, R⁴⁵, R⁴⁸, R⁴⁹, R⁵⁰, R⁵¹, R⁵² and R⁵³ each independently represent a hydrogen atom or a C₁₋₆ alkyl, C₂₋₆ hydroxyalkyl or a C₃₋₈ cycloalkyl group, or any of R²⁵ and R²⁶, R²⁷ and R²⁸, R³⁸ and R³⁹, R⁴¹ and R⁴², R⁴⁸ and R⁴⁹, R⁵⁰ and R⁵¹ together with the nitrogen atom to which they are both attached can form a 3- to 8-membered saturated heterocyclic ring; and R²⁹ is aryl.

20 Certain compounds of formula (IA) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (IA) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

25 As used herein, the term "halogen" includes fluorine, chlorine, bromine and iodine, and in particular is fluorine and chlorine. In the context of the present specification, unless otherwise indicated, an alkyl substituent or alkyl moiety in a substituent group may be linear or branched and may contain up to 10 carbon atoms. Examples of alkyl groups/moieties containing up to 7 carbon atoms include methyl, ethyl, n-propyl,
30 isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl and n-heptyl.

The term "cycloalkyl" refers to saturated alkyl rings, unless otherwise indicated containing from 3 to 9 and preferably from 4 to 7 carbon atoms. The term "heteroatom" includes oxygen, sulphur and nitrogen. The term "aryl" refers to aromatic groups such as phenyl or naphthyl, and in particular phenyl. "Carbocyclic" refers to saturated or unsaturated rings containing from 3 to 10 carbon atoms.

The expression "heterocyclic" includes saturated and unsaturated rings which unless otherwise indicated are of from 3 to 10 atoms, at least one of which is a heteroatom selected from oxygen, sulphur or nitrogen. The rings may be mono- or bicyclic, and saturated or unsaturated. Bicyclic rings may be fully or partially aromatic in character. Nitrogen heteroatoms will be substituted as necessary, and may also be in the form of N-oxides. Sulphur atoms may be in the form of S, S(O) or S(O)₂. In particular heterocyclic rings in compounds of formula (IA) and (IB) are saturated rings, such as piperidine, piperazine, pyrrolidine or homopiperidine.

A "hydroxyalkyl" substituent may contain one or more hydroxyl groups but preferably contains one hydroxyl group.

In formula (IA), each R¹ or R⁴ independently represents halogen or C₁-C₆, preferably C₁-C₄, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by at least one substituent (e.g. one, two or three substituents independently) selected from hydroxyl, halogen (e.g. chlorine, fluorine, bromine or iodine) and C₁-C₆, preferably C₁-C₄, alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy).

In an embodiment of the invention, in formula (IA) p is 0 or p is 1 and R¹ represents halogen, preferably chlorine, or R¹ represents methyl.

In an embodiment of the invention, in formula (IA) n is 1 or 2, preferably 1.

In an embodiment of the invention, in formula (IA) q is 0.

In an embodiment of the invention, in formula (IA) m is 1 or 0, preferably 0.

In formula (IA), within each grouping CR^5R^6 , R^5 and R^6 each independently represent hydrogen, halogen (e.g. chlorine, fluorine, bromine or iodine) or C_1 - C_6 , preferably C_1 - C_4 , alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl), or R^5 and R^6 together with the carbon atom to which they are both attached form a 3- to 6-membered cycloalkyl ring (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl).

10 In an embodiment of the invention, in formula (IA) R^5 and R^6 each independently represent hydrogen, C_1 - C_4 alkyl, preferably methyl, or R^5 and R^6 together with the carbon atom to which they are both attached form a cyclopropyl ring. Preferably each R^5 and R^6 is hydrogen.

15 In formula (IA), R^2 represents a 4- to 9-membered cycloalkyl ring system, which cycloalkyl ring system can be optionally substituted by at least one substituent (e.g. one, two, three or four substituents independently) independently selected from halogen (e.g. chlorine, fluorine, bromine or iodine), hydroxyl, $-S(O)_f C_{1-6}$ alkyl, $-NR^7R^8$, $-C(O)OR^{12}$, $-OC(O)R^{13}$, $-C(O)NR^{14}R^{15}$, $-SO_2NR^{16}R^{17}$, $-NR^{18}SO_2R^{19}$, C_{1-6} alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_{1-6} hydroxyalkyl (e.g. $-CH_2OH$, $-CH_2CH_2OH$, $-CH_2CH_2CH_2OH$ or $-CH(OH)CH_3$) or a C_{1-6} , preferably C_{1-4} , alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) which C_{1-6} alkyl group can be optionally substituted by at least one halogen (e.g. chlorine, fluorine, bromine or iodine); f is 0, 1 or 2.

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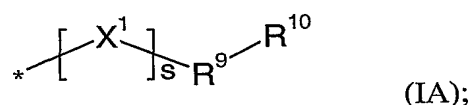
In formula (IA), preferred 4- to 9-membered cycloalkyl ring systems R^2 include cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

30 In formula (IA), preferred substituents on the 4- to 9-membered cycloalkyl ring system R^2 include halogen, hydroxyl, $-S(O)_f C_{1-6}$ alkyl and a C_{1-6} alkyl group.

In formula (IA), examples of groups $-S(O)_f C_{1-6}alkyl$ include methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, methylsulphonyl and ethylsulphonyl.

In an embodiment of the invention, in formula (IA) R^2 represents a cyclopentyl or
5 cyclohexyl ring optionally substituted with a C_{1-4} alkyl group.

In formula (IA), one of Y or Z is nitrogen and the other is a group CR^3 wherein R^3 is a group of formula (IIA)



10 wherein X^1 represents an oxygen or sulphur atom, or a group $>N-R^{11}$ wherein R^{11} is hydrogen or a C_{1-5} , preferably C_{1-4} , alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl) which can be optionally substituted by one or more substituents (e.g. one, two, three or four substituents independently) selected from hydroxyl, halogen (e.g. chlorine, fluorine, bromine or iodine), or C_{1-6} , preferably
15 C_{1-4} , alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy); s is 0 or 1.

In an embodiment of the invention, in formula (IA) Y is nitrogen and Z is a group CR^3 .

In formula (IIA), R^9 represents a bond or a C_{1-5} , preferably C_{1-3} , alkylene group (e.g. -
20 CH_2 -, $-CH_2CH_2$ - or $-CH_2CH_2CH_2$ -), which can be optionally substituted by at least one substituent (e.g. one, two, three or four substituents independently) selected from hydroxyl, halogen (e.g. chlorine, fluorine, bromine or iodine), or C_{1-6} , preferably C_{1-4} , alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy).

25 In formula (IIA), R^{10} represents hydrogen, hydroxyl, carboxyl, $-C(O)OR^{20}$, $-NR^{21}R^{22}$, $-C(O)NOH$, or a group $-WR^{23}$;

or R^{10} represents a 4- to 9-membered carbocyclic or heterocyclic ring, either of which may include bridging groups, which carbocyclic and heterocyclic ring can be optionally
30 substituted by at least one substituent (e.g. one, two, three or four substituents

independently) selected from halogen (e.g. chlorine, fluorine, bromine or iodine), hydroxyl, =O, carboxyl, cyano, C₁-C₆, preferably C₁₋₄, alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl), C₁₋₆, preferably C₁₋₄, hydroxyalkyl (e.g. -CH₂OH, -CH₂CH₂OH, -CH₂CH₂CH₂OH or -CH(OH)CH₃), a group

5 -W'R²⁴, -C(O)NOH, -(CH₂)_tNR²⁵R²⁶, -(CH₂)_tC(O)NR²⁷R²⁸, -(CH₂)_tR²⁹-(CH₂)_tNR³⁰C(O)R³¹, -S(O)_rR³², -NR³³SO₂R³⁴, -NR³⁵C(O)NR³⁶S(O)_rR³⁷, -S(O)_r(CH₂)_tNR³⁸R³⁹, -NR⁴⁰S(O)_rNR⁴¹R⁴², -S(O)_r(CH₂)_tC(O)OR⁴³, or M(CH₂)_tC(O)OR⁴⁴ wherein M represents a bond, O, S(O)_r, or a group >NR⁴⁵.

10 In an embodiment of the invention, in formula (IIA) t is 0, 1 or 2, preferably 0.

In an embodiment of the invention, in formula (IIA) R⁹ represents a C₁₋₅ alkylene group which can be optionally substituted by at least one hydroxyl; and R¹⁰ represents hydrogen, hydroxyl, carboxyl, -C(O)OR²⁰, -NR²¹R²², -C(O)NOH, or a group -WR²³.

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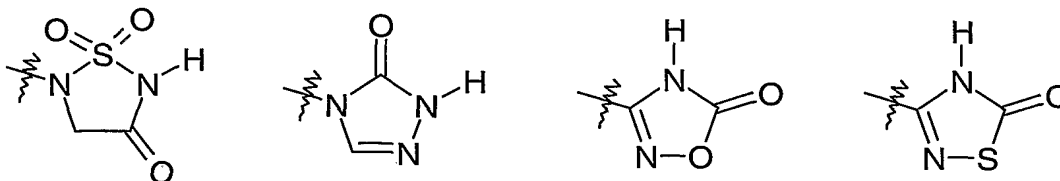
In formula (IIA), when R¹⁰ represents a 4- to 9-membered carbocyclic ring examples of preferred carbocyclic rings include cyclobutyl, cyclopentyl, cyclohexyl, most preferably cyclohexyl.

20 In formula (IIA), when R¹⁰ represents a 4- to 9-membered heterocyclic ring, the heterocyclic ring preferably contains from 1 to 3, more preferably 1 to 2, heteroatoms selected from nitrogen, oxygen and sulphur, preferably nitrogen: examples of preferred heterocyclic rings R¹⁰ in formula (IIA) include pyrrolidinyl, piperidinyl, piperazinyl, homopiperazinyl and homopiperidinyl.

25

In formula (IIA), when R¹⁰ represents a substituted 4- to 9-membered heterocyclic ring, examples of preferred substituents for the heterocyclic ring include hydroxyl, cyano, carboxyl, methyl, -NH₂, -NHCH₃, -NHCH₂CH₂OH, -CH₂C(O)OH, -NHCH₂C(O)OH, -NHCH₂CH₂C(O)OH, -CH₂NHCH₃, -CH₂NHCH₂CH₂OH, -SO₂CH₂CH₂OH, -

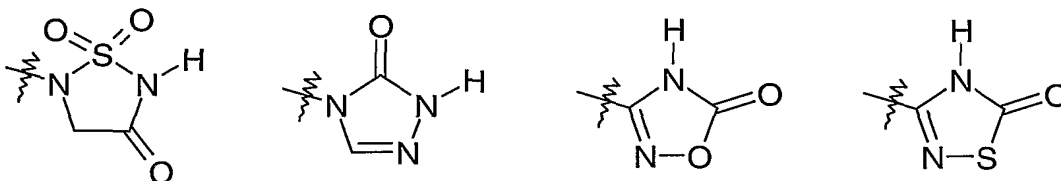
30 N(CH₂CH₂OH)C(O)OC(CH₃)₃, -NH SO₂CF₃, -NHC(O)NHSO₂CH₃, tetrazolyl and groups of formula:



In an embodiment of the invention, in formula (IIA) s is 0; R^9 is a bond; and R^{10} is an optionally substituted 4- to 9-membered carbocyclic or heterocyclic ring.

In an embodiment of the invention, when in formula (IIA) s is 0 and R^9 represents a bond, R^{10} represents a pyrrolidinyl, piperidinyl, piperazinyl or homopiperidinyl group, which can be optionally substituted by at least one substituent selected from hydroxyl, cyano, carboxyl, methyl, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_2OH$, $-CH_2C(O)OH$, $-NHCH_2C(O)OH$, $-NHCH_2CH_2C(O)OH$, $-CH_2NHCH_3$, $-CH_2NHCH_2CH_2OH$, $-SO_2CH_2CH_2OH$, $-N(CH_2CH_2OH)C(O)OC(CH_3)_3$, $-NH SO_2CF_3$, $-NHC(O)NHSO_2CH_3$.

In another embodiment of the invention, when in formula (IIA) s is 0 and R^9 represents a bond, R^{10} represents a pyrrolidinyl, piperidinyl, piperazinyl or homopiperidinyl group, which can be optionally substituted by at least one substituent selected from tetrazolyl and groups of formula:



In formula (IIA), R^{21} and R^{22} are independently selected from hydrogen, C_{2-7} alkenyl, C_{1-6} alkylcarbonyl (e.g. methylcarbonyl or ethylcarbonyl), $-SO_2R^{46}$ (e.g. SO_2CF_3), $-C(O)NHSO_2R^{47}$ (e.g. $-C(O)NHSO_2CH_3$), a 3- to 8-membered carbocyclic or heterocyclic ring which carbocyclic or heterocyclic ring can be optionally substituted by at least one substituent (e.g. one, two, three or four substituents independently) selected from halogen,

hydroxyl and carboxyl. When R^{21} and/or R^{22} represent a 3- to 8-membered heterocyclic ring, said ring preferably comprises from 1 to 3, more preferably 1 to 2, heteroatoms selected from nitrogen, oxygen and sulphur.

5 Alternatively, in formula (IIA) R^{21} and R^{22} may independently represent a C_{1-7} , preferably C_{1-4} alkyl group (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl) which C_{1-7} alkyl group can be optionally substituted by at least one substituent (e.g. one, two, three or four substituents independently) independently selected from halogen (e.g. chlorine, fluorine, bromine or iodine), carboxyl, hydroxyl, $-NH(CH_2)_{2-4}OH$, C_{1-6} ,
 10 preferably C_{1-4} , alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), C_{1-6} alkylthio (e.g. methylthio, ethylthio, n-propylthio or n-butylthio), C_{1-6} , preferably C_{1-4} , alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), $-NR^{48}R^{49}$, $-C(O)NR^{50}R^{51}$, $NR^{52}C(O)R^{53}$, $-NR^{54}SO_2R^{55}$ and $-NR^{67}C(O)NR^{68}SO_2R^{56}$.

15 In an embodiment of the invention, in formula (IIA) when s is 1 and R^9 is a bond, R^{10} is other than hydroxyl, carboxyl, $-C(O)OR^{20}$, $-NR^{21}R^{22}$, or $C(O)NOH$

In formula (IIA) in the groups $-WR^{23}$ and $-W'R^{24}$, W and W' preferably independently represent a bond, O, S, SO, SO_2 or $>NR^{61}$, most preferably a bond.

20 In formula (IIA), R^{23} and R^{24} independently represent a 3- to 10-, preferably 5 to 6-membered carbocyclic or heterocyclic ring comprising from 1 to 5, preferably 2 to 4, heteroatoms independently selected from nitrogen, oxygen and sulphur, which carbocyclic or heterocyclic ring can be optionally substituted with at least one substituent (e.g. one,
 25 two or three substituents independently) selected from hydroxyl, $=O$, $=S$, nitro, cyano, amino, halogen (e.g. chlorine, fluorine bromine or iodine), $-SO_2C_{1-6}$ alkyl, C_{1-6} alkylcarbonyl (e.g. methylcarbonyl or ethylcarbonyl), C_{1-6} alkoxycarbonyl (e.g. methoxycarbonyl or ethoxycarbonyl), C_{1-6} alkylamino (e.g. methylamino or ethylamino), di- C_{1-6} alkylamino (e.g. dimethylamino) and a C_{1-6} alkyl group (e.g. methyl, ethyl,
 30 n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) which C_{1-6} alkyl group can be optionally substituted by at least one substituent (e.g. one, two or three

substituents independently) selected from halogen (e.g. chlorine, fluorine bromine or iodine) and hydroxyl;

Examples of groups R^{23} and R^{24} that may be conveniently employed in the present invention in accordance with formula (IA) include:-

(I) tetrazolyl;

(II) a 5- to 6- membered carbocyclic or heterocyclic ring comprising from 1 to 4, preferably 1 to 3, heteroatoms selected from nitrogen, oxygen and sulphur, which carbocyclic or heterocyclic ring is substituted by at least one substituent (e.g. one, two or three substituents independently) selected from hydroxyl, =O, and =S and which carbocyclic or heterocyclic ring may further be optionally substituted by at least one substituent selected from halogen (e.g. chlorine, fluorine, bromine or iodine), nitro, cyano, $-SO_2C_{1-6}$ alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy carbonyl, and a C_{1-6} , preferably C_{1-4} , alkyl group which C_{1-6} alkyl group can be optionally substituted by at least one substituent (e.g. one, two or three substituents) selected from halogen (e.g. chlorine, fluorine, bromine or iodine), and hydroxyl;

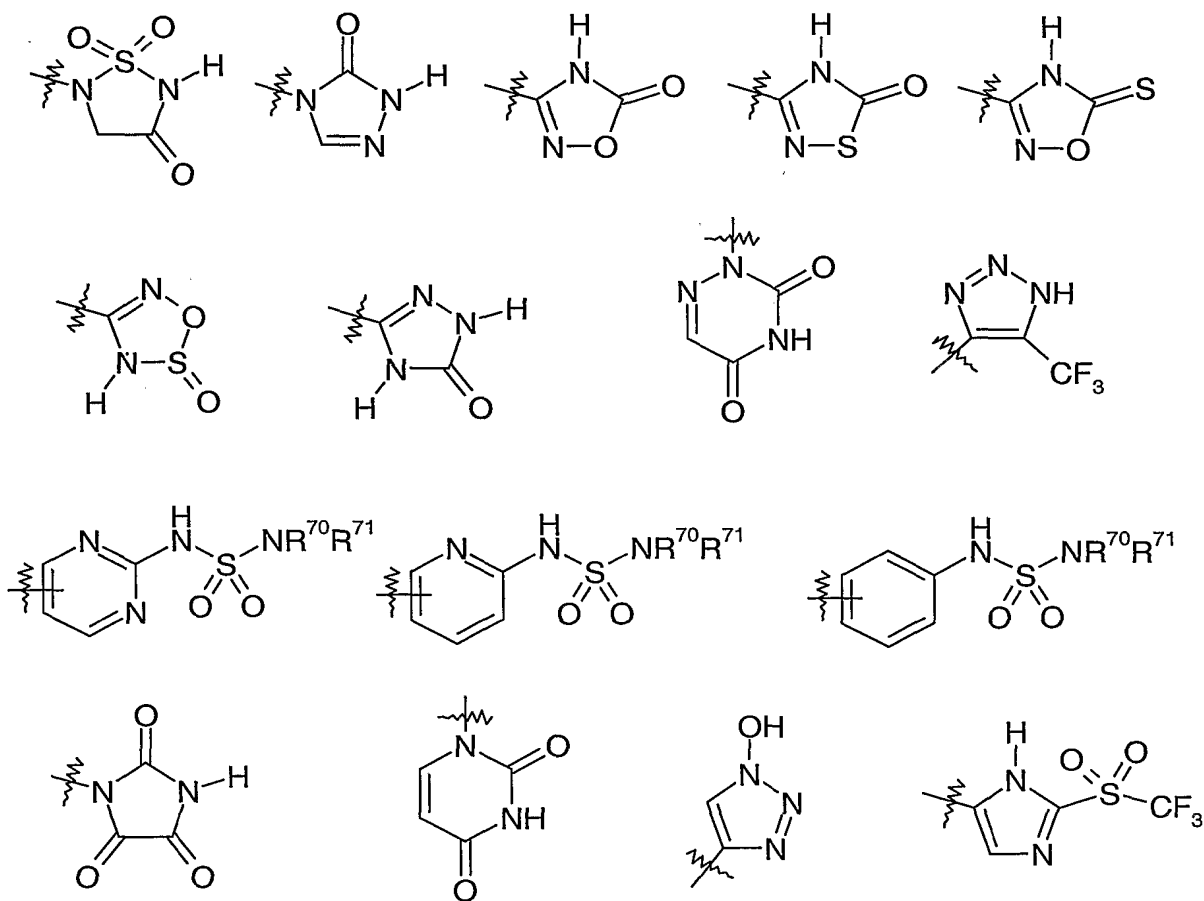
(III) a 1,2,3-triazolyl or 1,2,4 triazolyl group which triazolyl group can be optionally substituted by at least one substituent (e.g. one, two or three substituents) selected from halogen (e.g. chlorine, fluorine, bromine or iodine), nitro, cyano, $-SO_2C_{1-6}$ alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxy carbonyl and a C_{1-6} , preferably C_{1-4} , alkyl group which C_{1-6} alkyl group can be optionally substituted by at least one substituent (e.g. one, two or three substituents) selected from halogen (e.g. chlorine, fluorine, bromine or iodine), and hydroxyl; and

(IV) a phenyl group or a 5- to 6- membered unsaturated heterocyclic ring comprising from 1 to 2 nitrogen atoms, which phenyl group or heterocyclic ring is substituted by a group $-NR^{69}SO_2NR^{70}R^{71}$ or a group $-SO_2R^{72}$, wherein R^{69} , R^{70} , R^{71} and R^{72} each independently represent a hydrogen atom or a C_{1-6} , preferably C_{1-4} , alkyl group which C_{1-6} alkyl group can be optionally substituted by at least one substituent (e.g. one, two or three substituents) selected from halogen (e.g. chlorine, fluorine, bromine or iodine), and hydroxyl.

When in formula (IIA) R^{23} and/or R^{24} represent a 5- to 6- membered heterocyclic ring substituted by at least one substituent selected hydroxyl, =O or =S, nitrogen heteroatoms in the heterocyclic ring may carry hydroxyl substituents and sulphur atoms in the heterocyclic ring may be in the form of S, S(O) (i.e. carrying one oxo substituent) or S(O)₂ (i.e. carrying two oxo substituents).

When in formula (IIA), R^{23} and/or R^{24} represent a 5 to 6- membered unsaturated heterocyclic ring comprising from 1 to 2 nitrogen atoms and substituted by a group $-NR^{69}$ $SO_2NR^{70}R^{71}$ or a group $-SO_2R^{72}$, examples of preferred heterocyclic rings include pyridinyl, pyrimidinyl and imidazolyl.

In formula (IIA), examples of groups $-R^{23}$ and $-R^{24}$ include:



In an embodiment of the invention, in formula (IIA) R^{10} represents $-WR^{23}$ or R^{10} represents a 4- to 9-membered carbocyclic or heterocyclic ring, either of which may include bridging groups, which carbocyclic and heterocyclic ring is substituted by at least one substituent - $W'R^{24}$. In this embodiment W, W' , R^{23} and R^{24} are as defined herein above.

5

In an embodiment of the invention, R^{23} and R^{24} are independently selected from tetrazolyl or a 5- to 6- membered carbocyclic or heterocyclic ring comprising from 1 to 3 heteroatoms selected from nitrogen, oxygen and sulphur, which carbocyclic or heterocyclic ring is substituted by at least one substituent selected from hydroxyl, =O, and =S. In a further aspect of this embodiment, W and W' represent a bond.

10

In formula (IA), R^7 , R^8 , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} and R^{19} each independently represent a hydrogen atom or C_{1-6} , preferably C_{1-4} , alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) optionally substituted by at least one substituent (e.g. one, two or three substituents independently) selected from hydroxyl, halogen (e.g. chlorine, fluorine, bromine or iodine), and C_{1-6} , preferably C_{1-4} , alkoxy (e.g. methoxy, ethoxy, n-propoxy or n-butoxy), or any of R^7 and R^8 , R^{14} and R^{15} , R^{16} and R^{17} together with the nitrogen atom to which they are both attached can form a 3- to 8-membered saturated heterocyclic ring (e.g. a pyrrolidine or piperazine ring).

15

20

In formula (IA), R^{20} , R^{34} , R^{37} , R^{46} , R^{47} , R^{54} , R^{55} , R^{56} , R^{57} , R^{58} , R^{59} , R^{60} , R^{61} , R^{62} , R^{63} , R^{64} , R^{65} and R^{66} each independently represent hydrogen or a C_{1-6} , preferably C_{1-4} , alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl or n-hexyl) which can be optionally substituted by at least one substituent (e.g. one, two or three substituents independently) selected from halogen (e.g. chlorine, fluorine, bromine or iodine), and hydroxyl.

25

In formula (IA), R^{25} , R^{26} , R^{27} , R^{28} , R^{30} , R^{31} , R^{32} , R^{33} , R^{35} , R^{36} , R^{38} , R^{39} , R^{40} , R^{41} , R^{42} , R^{43} , R^{44} , R^{45} , R^{48} , R^{49} , R^{50} , R^{51} , R^{52} and R^{53} each independently represent a hydrogen atom or a C_{1-6} , preferably C_{1-4} , alkyl (e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-

30

butyl, n-pentyl), C₂₋₆, preferably C₁₋₄, hydroxyalkyl (e.g. -CH₂CH₂OH, -CH₂CH₂CH₂OH or -CH(OH)CH₃), or a C₃₋₈, preferably C₄₋₆, cycloalkyl group (e.g. cyclobutyl, cyclopentyl and cyclohexyl), or any of R²⁵ and R²⁶, R²⁷ and R²⁸, R³⁸ and R³⁹, R⁴¹ and R⁴², R⁴⁸ and R⁴⁹, R⁵⁰ and R⁵¹ together with the nitrogen atom to which they are both attached
 5 can form a 3- to 8-membered saturated heterocyclic ring (e.g. a pyrrolidine or piperazine ring); R²⁹ is aryl (e.g. phenyl).

In formula (IIA), any hydroxyl groups will not normally be attached to a carbon atom adjacent a nitrogen atom. Further, when R⁹ is other than a bond, the group R¹⁰ may be
 10 attached to the C₁-C₅ alkyl moiety of R⁹ at any suitable point; thus R¹⁰ may be attached to an internal or terminal carbon atom of the C₁-C₅ alkyl moiety of R⁹.

In an embodiment of the invention, there is provided a compound of formula (IA) or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

15 p is 0 or 1;

R¹ represents halogen or methyl;

q is 0;

X is -C(O)NH- or -NHC(O)-;

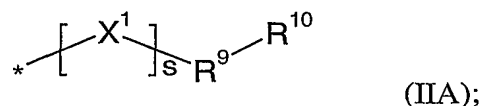
n is 0, 1, 2 or 3;

20 m is 0;

within each grouping CR⁵R⁶, R⁵ and R⁶ each independently represent hydrogen or a C₁₋₄ alkyl group or R⁵ and R⁶ together with the carbon atom to which they are both attached can form a cyclopropyl ring;

R² represents a 4- to 7-membered cycloalkyl ring optionally substituted with a C₁₋₄ alkyl group which alkyl group can be optionally substituted with 1 to 3 halogen atoms;

25 Y is nitrogen and Z is a group CR³ wherein R³ is a group of formula (IIA)



s is 0 or 1;

X¹ is a group >N-R¹¹ wherein R¹¹ is hydrogen or a C₁₋₄ alkyl group;

30 R⁹ represents a bond or a C₁₋₅ alkylene group optionally substituted by hydroxyl;

- R^{10} represents hydrogen, hydroxyl, carboxyl, $-C(O)OR^{20}$, $-NR^{21}R^{22}$ or $C(O)NOH$, or R^{10} represents a 4- to 9-membered carbocyclic or heterocyclic ring which heterocyclic ring comprises 1 or 2 nitrogen atoms and which carbocyclic or heterocyclic ring can be optionally substituted by at least one substituent selected from halogen, carboxyl, cyano, C₁-C₆ alkyl, C₁-C₆ hydroxyalkyl, $-C(O)NOH$, $-(CH_2)_tNR^{25}R^{26}$, $-(CH_2)_tC(O)NR^{27}R^{28}$, $-(CH_2)_tR^{29}-(CH_2)_tNR^{30}C(O)R^{31}$, $NR^{33}SO_2R^{34}$, $NR^{35}C(O)NR^{36}S(O)_rR^{37}$, $-S(O)_r(CH_2)_tNR^{38}R^{39}$, $-S(O)_r(CH_2)_tC(O)OR^{43}$, or $M(CH_2)_tC(O)OR^{44}$ wherein M represents a bond, O, or a group $>NR^{45}$;
- t is 0, 1 or 2;
- r is 0, 1 or 2;
- R^{21} and R^{22} are independently selected from hydrogen, C₂₋₇ alkenyl, C₁₋₆ alkylcarbonyl, $-SO_2R^{46}$, $-C(O)NHSO_2R^{47}$, or R^{21} and R^{22} may independently represent a C₁₋₇ alkyl group which C₁₋₇ alkyl group can be optionally substituted by at least one substituent independently selected from halogen, carboxyl, hydroxyl, $-NH(CH_2)_{2-4}OH$, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ alkoxy carbonyl, $-NR^{48}R^{49}$, $-C(O)NR^{50}R^{51}$, $NR^{52}COR^{53}$, $-NR^{54}SO_2R^{55}$ and $-NR^{67}C(O)NR^{68}SO_2R^{56}$; and
- R^{25} , R^{26} , R^{27} , R^{28} , R^{30} , R^{31} , R^{32} , R^{33} , R^{35} , R^{36} , R^{38} , R^{39} , R^{43} , R^{44} , R^{45} , R^{48} , R^{49} , R^{50} , R^{51} , R^{52} and R^{53} each independently represent a hydrogen atom, a C₁₋₆ alkyl group or a C₂₋₆ hydroxyalkyl group; R^{29} is aryl; and R^{34} , R^{37} , R^{46} , R^{47} , R^{54} , R^{55} , R^{56} , R^{67} and R^{68} each independently represent hydrogen or a C₁₋₆ alkyl group which can be optionally substituted by at least one substituent selected from halogen and hydroxyl.

In a further embodiment of the invention, there is provided a compound of formula (IA) or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

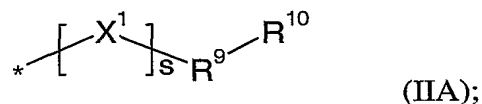
- p is 0 or 1;
- R^1 represents halogen or methyl;
- q is 0;
- X is $-C(O)NH-$ or $-NHC(O)-$;
- n is 0, 1, 2 or 3;
- m is 0;

within each grouping CR^5R^6 , R^5 and R^6 each independently represent hydrogen or a C_{1-4} alkyl group or R^5 and R^6 together with the carbon atom to which they are both attached can form a cyclopropyl ring;

R^2 represents a 4- to 7-membered cycloalkyl ring optionally substituted with a C_{1-4} alkyl

5 group which alkyl group can be optionally substituted with 1 to 3 halogen atoms;

Y is nitrogen and Z is a group CR^3 wherein R^3 is a group of formula (IIA)



s is 0 or 1;

X^1 is a group $>N-R^{11}$ wherein R^{11} is hydrogen or a C_{1-4} alkyl group;

10 R^9 represents a bond or a C_{1-5} alkylene group optionally substituted by hydroxyl;

R^{10} represents a group $-WR^{23}$, or R^{10} represents a 4- to 9-membered carbocyclic or heterocyclic ring which heterocyclic ring comprises 1 or 2 nitrogen atoms, and which carbocyclic or heterocyclic ring is substituted by at least one substituent $-W'R^{24}$ and may further be optionally substituted by at least one substituent selected from halogen or

15 C_1-C_6 alkyl;

W and W' independently represent a bond; and

R^{23} and R^{24} independently represent a group selected from: tetrazolyl;

a 5- to 6- membered carbocyclic or heterocyclic ring comprising from 1 to 3 heteroatoms selected from nitrogen, oxygen and sulphur, which carbocyclic or heterocyclic ring is

20 substituted by at least one substituent selected from hydroxyl, =O, and =S and which

carbocyclic or heterocyclic ring may further be optionally substituted by at least one substituent selected from halogen, nitro, cyano, $-SO_2C_{1-6}$ alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl, and a C_{1-6} alkyl group which C_{1-6} alkyl group can be optionally substituted by at least one substituent selected from halogen and hydroxyl;

25 a 1,2,3-triazolyl or 1,2,4 triazolyl group which triazolyl group can be optionally substituted by at least one substituent selected from halogen, nitro, cyano, $-SO_2C_{1-6}$ alkyl, C_{1-6} alkylcarbonyl, C_{1-6} alkoxycarbonyl and C_{1-6} alkyl;

a phenyl group or a 5- to 6- membered unsaturated heterocyclic ring comprising from 1 to 2 nitrogen atoms, which phenyl group or heterocyclic ring is substituted by a group $-NR^{69}$

30 $SO_2NR^{70}R^{71}$ or a group $-SO_2R^{72}$, wherein R^{69} , R^{70} , R^{71} and R^{72} each independently represent a hydrogen atom or a C_{1-6} , preferably C_{1-4} , alkyl group which C_{1-6} alkyl group

can be optionally substituted by at least one substituent (e.g. one, two or three substituents) selected from halogen (e.g. chlorine, fluorine, bromine or iodine), and hydroxyl.

In a further embodiment of the invention, there is provided a compound of formula (IA) or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein:

p is 0 or 1;

R¹ represents halogen or methyl;

q is 0;

X is -C(O)NH- or -NHC(O)-;

n is 1 or 2,

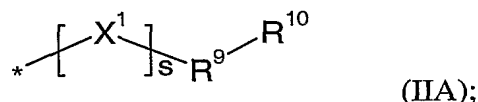
m is 0;

within each grouping CR⁵R⁶, R⁵ and R⁶ each independently represent hydrogen or a C₁₋₄ alkyl group;

R² represents a 5 or 6-membered cycloalkyl ring optionally substituted with a C₁₋₄ alkyl

group;

Y is nitrogen and Z is a group CR³ wherein R³ is a group of formula (IIA)



s is 0;

R⁹ represents a bond; and

R¹⁰ represents a 4- to 9-membered heterocyclic ring, which heterocyclic ring comprises 1 or 2 nitrogen atoms, and which heterocyclic ring can be optionally substituted by at least one substituent selected from hydroxyl, cyano, carboxyl, methyl, -NH₂, -NHCH₃, -NHCH₂CH₂OH, -CH₂C(O)OH, -NHCH₂C(O)OH, -NHCH₂CH₂C(O)OH, -CH₂NHCH₃, -CH₂NHCH₂CH₂OH, -SO₂CH₂CH₂OH, -N(CH₂CH₂OH)C(O)OC(CH₃)₃, -NHSO₂CF₃, -NHC(O)NHSO₂CH₃.

In a further embodiment of the invention the compound of formula (IA) is

N-[6-Chloro-2-(4-piperidinylmethyl)-5-quinolinyl]-cyclohexaneacetamide, dihydrochloride,

N-[6-Chloro-2-(1-piperazinyl)-5-quinolinyl]-cyclohexaneacetamide, dihydrochloride,

N-[6-Chloro-2-[methyl[3-(methylamino)propyl]amino]-5-quinoliny]-
cyclohexaneacetamide, dihydrochloride,
6-Chloro-*N*-(cyclohexylmethyl)-2-methyl-5-quinolinecarboxamide, hydrochloride,
N-[6-Chloro-2-[(3-hydroxypropyl)amino]-5-quinoliny]-cyclohexaneacetamide,
5 hydrochloride,
N-[6-Chloro-2-[(2*R*)-2,3-dihydroxypropyl]amino]-5-quinoliny]-
cyclohexaneacetamide,
4-[[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinoliny]amino]-butanoic acid,
N-[6-Chloro-2-[methyl[3-(methylamino)propyl]amino]-5-quinoliny]-4-
10 (trifluoromethyl)-cyclohexaneacetamide, dihydrochloride,
N-[6-Chloro-2-(1-piperaziny)-5-quinoliny]-4-(trifluoromethyl)-
cyclohexaneacetamide,
N-[6-Chloro-2-(hexahydro-1*H*-1,4-diazepin-1-yl)-5-quinoliny]-
cyclohexaneacetamide,
15 *N*-[6-Chloro-2-[(*cis*-3,5-dimethyl-1-piperaziny)-5-quinoliny]-
cyclohexaneacetamide,
N-[6-Chloro-2-(4-methyl-1-piperaziny)-5-quinoliny]-cyclohexaneacetamide,
dihydrochloride,
N-[6-Chloro-2-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-5-quinoliny]-
20 cyclohexaneacetamide, acetate,
N-[6-Chloro-2-[(3*R*)-3-pyrrolidinylamino]-5-quinoliny]-cyclohexaneacetamide,
dihydrochloride,
N-[2-[3-(Ethylamino)propyl]-6-methyl-5-quinoliny]-cyclohexaneacetamide,
dihydrochloride,
25 *N*-[6-Chloro-2-[3-(ethylamino)propyl]-5-quinoliny]-cyclohexaneacetamide,
dihydrochloride,
N-[6-Chloro-2-[[2-[(2-hydroxyethyl)amino]ethyl]amino]-5-quinoliny]-
cyclohexaneacetamide, dihydrochloride,
N-5-Quinoliny-cyclohexaneacetamide,
30 1-Methyl-*N*-5-quinoliny-cyclohexaneacetamide,
4-Methyl-*N*-5-quinoliny-cyclohexaneacetamide,
N-5-Quinoliny-cyclopentanepropanamide,

N-[6-Chloro-2-[3-[(3-hydroxypropyl)amino]propyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[2-(3-Aminopropyl)-6-chloro-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-[3-[[[(methylsulfonyl)amino]carbonyl]amino]propyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[2-[3-(Butylamino)propyl]-6-chloro-5-quinolinyl]-cyclohexaneacetamide dihydrochloride,

N-[6-Chloro-2-[methyl[3-(methylamino)propyl]amino]-5-quinolinyl]-1-cyclohexyl-cyclopropanecarboxamide, hydrochloride,

N-[6-Chloro-2-(1-piperazinyl)-5-quinolinyl]-1-cyclohexyl-cyclopropanecarboxamide,

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-[(3*S*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[2-[(3*R*)-3-Amino-1-pyrrolidinyl]-6-chloro-5-quinolinyl]-cyclohexaneacetamide,

N-[2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-chloro-5-quinolinyl]-cyclohexaneacetamide,

N-[2-(4-Amino-1-piperidinyl)-6-chloro-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-[(3*R*)-3-(methylamino)-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-[(3*R*)-3-[(2-hydroxyethyl)amino]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-[(3*S*)-3-(methylamino)-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-piperidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-methyl-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Methyl-2-(1-piperazinyl)-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-glycine,

N-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]- β -alanine,

6-Chloro-*N*-(cyclohexylmethyl)quinoline-5-carboxamide,
6-Chloro-*N*-(cyclohexylmethyl)-2-(1-piperazinyl)-5-quinolinecarboxamide,
dihydrochloride,
2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-chloro-*N*-(cyclohexylmethyl)-5-
5 quinolinecarboxamide,
6-Chloro-*N*-(cyclohexylmethyl)-2-[methyl[3-(methylamino)propyl]amino]-5-
quinoline carboxamide, dihydrochloride,
6-Chloro-*N*-(cyclohexylmethyl)-2-[methyl[2-(methylamino)ethyl]amino]-5-
quinolinecarboxamide, dihydrochloride,
10 6-Chloro-*N*-(cyclohexylmethyl)-2-[3-[(3-hydroxypropyl)amino]propyl]-5-
quinolinecarboxamide,
2-[(3*R*)-3-Amino-1-pyrrolidinyl]-6-chloro-*N*-(cyclohexylmethyl)-5-
quinolinecarboxamide, dihydrochloride,
N-(2-Amino-6-chloro-5-quinoliny)-cyclohexaneacetamide, trifluoroacetate,
15 6-Chloro-*N*-(cyclohexylmethyl)-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-
pyrrolidinyl]-5-quinolinecarboxamide, hydrochloride,
2-[(3*S*)-3-Amino-1-piperidinyl]-6-chloro-*N*-(cyclohexylmethyl)-5-
quinolinecarboxamide,
6-Chloro-*N*-(cyclohexylmethyl)-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-piperidinyl]-
20 5-quinolinecarboxamide, hydrochloride,
6-Chloro-*N*-(cyclohexylmethyl)-2-(3-hydroxy-1-azetidiny)- 5-
quinolinecarboxamide,
2-[(3*S*)-3-Amino-1-pyrrolidinyl]-*N*-(cyclohexylmethyl)-5-quinolinecarboxamide,
6-Chloro-*N*-(cyclohexylmethyl)-2-[3-[(2-hydroxyethyl)amino]-1-azetidiny]- 5
25 quinolinecarboxamide,
[1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinoliny]-3-pyrrolidinyl](2-
hydroxyethyl)-carbamic acid 1,1-dimethylethyl ester,
N-(Cyclohexylmethyl)-6-methyl-5-quinolinecarboxamide,
2-[(3*S*)-3-Amino-1-pyrrolidinyl]-*N*-(cyclohexylmethyl)-6-methyl-5-
30 quinolinecarboxamide, acetate,
N-[2-[[3*S*)-3-Amino-1-pyrrolidinyl]methyl]-6-chloro-5-quinoliny]-
cyclohexaneacetamide,

N-[2-[(3*S*)-3-Amino-1-piperidinyl]-6-chloro-5-quinolinyl]-cyclohexaneacetamide,
N-[6-Chloro-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-piperidinyl]-5-quinolinyl]-
cyclohexaneacetamide,

N-[2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-chloro-5-quinolinyl]-
5 cyclopentanepropanamide,

N-[6-Chloro-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-pyrrolidinyl]-5-quinolinyl]-
cyclopentanepropanamide,

N-[6-Chloro-2-[4-(1,5-dihydro-5-oxo-4*H*-1,2,4-triazol-4-yl)-1-piperidinyl]-5-
quinolinyl]-cyclohexaneacetamide,

10 1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-D-proline, trifluoroacetate,
1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-4-piperidinecarboxylic
acid, lithium salt,

6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinebutanoic acid,

15 1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-4-piperidineacetic acid,
4-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-1-piperazineacetic acid,
lithium salt,

6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinepentanoic acid, 1-[6-Chloro-5-
[[cyclohexylmethyl)amino]carbonyl]-2-quinolinyl]-D-proline,

1-[6-Chloro-5-[[cyclohexylmethyl)amino]carbonyl]-2-quinolinyl]-L-proline,
20 trifluoroacetate,

4-[6-Chloro-5-[[cyclohexylmethyl)amino]carbonyl]-2-quinolinyl]-1-
piperazineacetic acid, acetate,

1-[6-Chloro-5-[[cyclohexylmethyl)amino]carbonyl]-2-quinolinyl]-4-
piperidinecarboxylic acid, sodium salt,

25 1-[6-Chloro-5-[[cyclohexylmethyl)amino]carbonyl]-2-quinolinyl]-4-
piperidineacetic acid, trifluoroacetate,

1-[6-Chloro-5-[(2-cyclohexylethyl)amino]carbonyl]-2-quinolinyl]-4-
piperidinecarboxylic acid,

1-[6-Chloro-5-[(3-cyclopentyl-1-oxopropyl)amino]-2-quinolinyl]-4-
30 piperidinecarboxylic acid,

1-[6-Chloro-5-[(3-cyclohexyl-1-oxopropyl)amino]-2-quinolinyl]-4-
piperidinecarboxylic acid, potassium salt,

1-[6-Chloro-5-[(1-methylcyclohexyl)acetyl]amino]-2-quinoliny]-4-piperidinecarboxylic acid,

N-[6-Chloro-2-[3-[(2-hydroxyethyl)amino]-1-piperidiny]-5-quinoliny]-cyclohexaneacetamide,

5 *N*-[6-Chloro-2-[2-[(2-hydroxyethyl)amino]methyl]-1-pyrrolidiny]-5-quinoliny]-cyclohexaneacetamide,

N-[6-Chloro-2-[3-(methylamino)-1-piperidiny]-5-quinoliny]-cyclohexaneacetamide,

10 *N*-[6-Chloro-2-[2-[(methylamino)methyl]-1-pyrrolidiny]-5-quinoliny]-cyclohexaneacetamide,

N-[2-[(3*R*)-3-Hydroxy-1-pyrrolidiny]-6-methyl-5-quinoliny]-cyclohexaneacetamide,

N-[(3*S*)-1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinoliny]-3-pyrrolidiny]-glycine,

15 *N*-[2-[(3*S*)-3-[(2-Hydroxyethyl)amino]-1-pyrrolidiny]-6-methyl-5-quinoliny]-cyclohexaneacetamide,

N-[(3*S*)-1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinoliny]-3-pyrrolidiny]- β -alanine,

20 *N*-[6-Chloro-2-[(3*S*)-3-[[trifluoromethyl]sulfonyl]amino]-1-pyrrolidiny]-5-quinoliny]-cyclohexaneacetamide,

N-[6-Chloro-2-[(3*S*)-3-[[[(methylsulfonyl)amino]carbonyl]amino]-1-pyrrolidiny]-5-quinoliny]-cyclohexaneacetamide,

N-[2-[(3*S*)-3-Amino-1-pyrrolidiny]-6-chloro-5-quinoliny]-cyclohexanepropanamide,

25 *N*-[6-Chloro-2-[methyl[3-(methylamino)propyl]amino]-5-quinoliny]-cyclohexanepropanamide,

N-[6-Chloro-2-(1-piperaziny)-5-quinoliny]-cyclohexanepropanamide,

N-[6-Chloro-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-pyrrolidiny]-5-quinoliny]-cyclohexanepropanamide,

30 2-[(3*S*)-3-Amino-1-pyrrolidiny]-6-chloro-*N*-(2-cyclohexylethyl)-5-quinolinecarboxamide, ditrifluoroacetate,

N-[6-Chloro-2-[(3*S*)-3-[(2-hydroxyethyl)sulfonyl]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-[(3*S*)-3-cyano-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[1-[6-Chloro-5-[[cyclohexylmethyl]amino]carbonyl]-2-quinolinyl]-3-azetidiny]- β -alanine,

6-Chloro-*N*-(cyclohexylmethyl)-2-[3-(1*H*-tetrazol-5-yl)-1-azetidiny]-5-quinolinecarboxamide,

N-[6-Chloro-2-[(3*S*)-3-(1*H*-tetrazol-5-yl)-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-[(3*R*)-3-(1*H*-tetrazol-5-yl)-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-[(3*S*)-3-[[2-(2*H*-tetrazol-5-yl)ethyl]amino]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-[4-(4,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)-1-piperidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-[4-(4,5-dihydro-5-oxo-1,2,4-thiadiazol-3-yl)-1-piperidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-[3-(1*H*-tetrazol-5-yl)propyl]-5-quinolinyl]-cyclohexaneacetamide, trifluoroacetate,

N-[6-Chloro-2-[4-(1*H*-tetrazol-5-yl)butyl]-5-quinolinyl]-cyclohexaneacetamide, 6-Chloro-*N*-(cyclohexylmethyl)-2-[4-(1*H*-tetrazol-5-yl)butyl]-5-quinolinecarboxamide,

N-[6-Chloro-2-[(3*S*)-3-[2-(1*H*-tetrazol-5-yl)ethoxy]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-[(3*S*)-3-[2-(4,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)ethoxy]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-[4-(1*H*-tetrazol-5-yl)-1-piperidinyl]-5-quinolinyl]cyclohexaneacetamide,

6-Chloro-*N*-(cyclohexylmethyl)-2-[4-(1*H*-tetrazol-5-yl)-1-piperidinyl]-5-quinolinecarboxamide,

6-Chloro-*N*-(2-cyclohexylethyl)-2-[4-(1*H*-tetrazol-5-yl)-1-piperidinyl]-5-quinolinecarboxamide,

6-Chloro-*N*-(cyclohexylmethyl)-2-[(3*S*)-3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-1-pyrrolidinyl]-5-quinolinecarboxamide,

N-[6-Chloro-2-(4-cyano-1-piperidinyl)-5-quinolinyl]-cyclohexaneacetamide, or
N-[6-Chloro-2-[4-[[[(trifluoromethyl)sulfonyl]amino]-1-piperidinyl]-5-quinolinyl]-
5 cyclohexaneacetamide.

or a pharmaceutically acceptable salt, prodrug or solvate of anyone thereof.

Pharmaceutically acceptable salts of compounds of formula (IA) that may conveniently be employed include base salts such as an alkali metal salt for example sodium, an alkaline
10 earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, procaine, dibenzylamine, *N,N*-dibenzylethylamine or amino acids for example lysine. In another aspect, where the compound is sufficiently basic, suitable salts include acid addition salts
15 such as methanesulphonate, fumarate, hydrochloride, hydrobromide, citrate, maleate and salts formed with phosphoric and sulphuric acid. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. A preferred pharmaceutically acceptable salt is a hydrochloride or sodium salt.

Prodrugs of compounds of formula (IA) that may conveniently be employed are
20 compounds which are hydrolysed *in vivo* to form compounds of formula (IA). Thus for example where compounds of formula (IA) include a carboxy group, these may be in the form of pharmaceutically acceptable esters or amides.

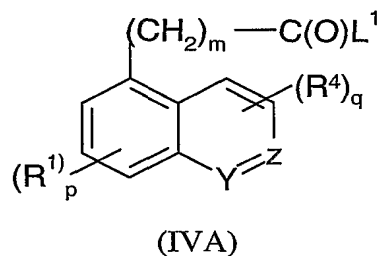
Pharmaceutically acceptable esters of formula (IA) for carboxyl groups include
25 C₁₋₆alkyl esters, for example methyl or ethyl; C₁₋₆alkoxymethyl esters, for example methoxymethyl; C₁₋₆alkanoyloxymethyl esters, for example pivaloyloxymethyl; phthalidyl esters; C₃₋₈cycloalkoxycarbonyloxyC₁₋₆alkyl esters, for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolan-2-ylmethyl esters, for example 5-methyl-1,3-dioxolan-2-ylmethyl; C₁₋₆alkoxycarbonyloxyethyl esters, for example
30 1-methoxycarbonyloxyethyl; aminocarbonylmethyl esters and mono- or di-*N*-(C₁₋₆alkyl) versions thereof, for example *N,N*-dimethylaminocarbonylmethyl esters and *N*-ethylaminocarbonylmethyl esters; and may be formed at any carboxy group in

the compounds of this invention. An *in vivo* cleavable ester of a compound of the invention containing a hydroxy group is, for example, a pharmaceutically-acceptable ester which is cleaved in the human or animal body to produce the parent hydroxy group. Pharmaceutically acceptable esters for hydroxy include C₁₋₆alkanoyl esters, for example acetyl esters; and benzoyl esters wherein the phenyl group may be substituted with aminomethyl or N- substituted mono- or di- C₁₋₆alkyl aminomethyl, for example 4-aminomethylbenzoyl esters and 4-N,N-dimethylaminomethylbenzoyl esters.

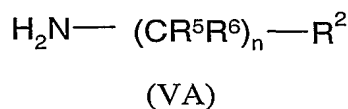
Pharmaceutically acceptable amides are similarly *in-vivo* hydrolysable to yield the parent acid, and include C₁₋₆alkylamides such as acetamide.

The present invention further provides a process for the preparation of a compound of formula (IA) as defined above, or a pharmaceutically acceptable salt, prodrug or solvate thereof, which comprises either:

(a) reacting a compound of formula (IVA)



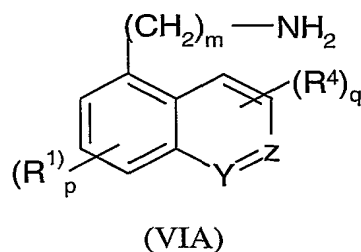
wherein L¹ represents a leaving group (e.g. hydroxyl or halogen) and Y, Z, R¹, R⁴, m, p and q are as defined in formula (IA), with a compound of formula (VA),



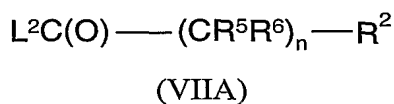
R², R⁵, R⁶ and n are as defined in formula (IA); or

(b) reacting a compound of formula (VIA)

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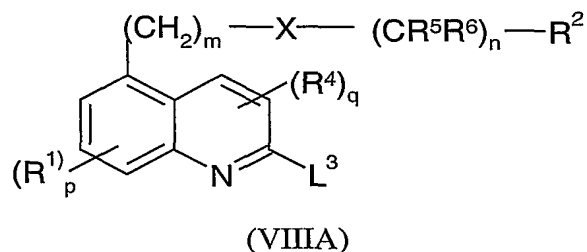


- 5 wherein Y, Z, R¹, R⁴, m, p and q are as defined in formula (IA), with a compound of formula (VIA)



- 10 wherein L² represents a leaving group (e.g. hydroxyl or halogen) and R², R⁵, R⁶ and n are as defined in formula (IA); or

- (c) when Y is N and Z is CR³, and R³ represents a group of formula (IIA) above where s is 1 and X is >NR¹¹, reacting a compound of formula (VIII A)

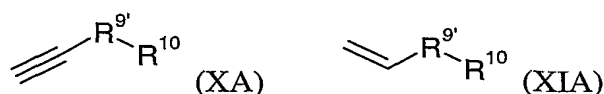


15

- wherein L³ is a leaving group (e.g. halogen, paratoluene sulphonate or methane sulphonate), and all other variables are as defined in relation to formula (IA), with a compound of formula (IXA), H-N(R¹¹)-R⁹-R¹⁰, wherein R⁹, R¹⁰ and R¹¹ are as defined in
- 20 formula (IIA); or

- (d) when Y is N and Z is CR³, and R³ is a group formula (IIA) wherein s is 0 and R⁹ is a C₁-C₅ alkylene group which may be optionally substituted as defined herein above with respect to formula (IA), reacting a compound of formula (VIII A) as defined in (c) above
- 25 with a compound of formula (XA) or (XIA)

27



wherein wherein $\text{R}^{9'}$ is suitably defined such that saturation of the alkene or alkyne and combination with $\text{R}^{9'}$ gives a group of formula R^9 as defined in formula (IIA), optionally followed by a hydrogenation reaction; or

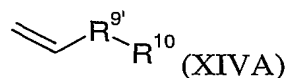
(e) when Y is N and Z is CR^3 , and R^3 is a group of formula (IIA) where s is 0, R^9 is $(\text{CH}_2)_2$ and R^{10} is $-\text{NR}^{21}\text{R}^{22}$, reacting a compound of formula (VIIA) as defined in (c) above with a compound of formula (XIIA)



wherein L^4 is a leaving group (eg. trialkyltin, dialkylboron or zinc), followed by reaction with a compound of formula (XIIIA), $\text{HNR}^{21}\text{R}^{22}$, wherein R^{21} and R^{22} are as defined above;

15 (f) when Y is N and Z is CR^3 , and R^3 is a group of formula (IIA) where s is 0, R^9 is $(\text{CH}_2)_2$ and R^{10} is $-\text{NR}^{19}\text{R}^{20}$, reacting a compound of formula (VIIIA) as defined in (c) above with a compound of formula (XIIA) as defined in (e) above, followed by an oxidation reaction and then by reaction with a compound of formula (XIIIA) as defined in (e) above under reductive amination conditions; or

20 (g) when Y is N and Z is CR^3 , and R^3 is a group of formula (IIA) where s is 0, reacting a compound of formula (VIIIA) as defined in (c) above with a compound of formula (XIVA)

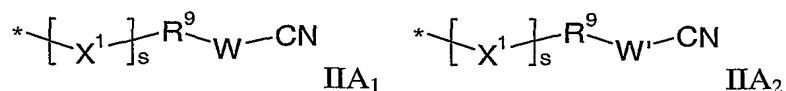


25 wherein $\text{R}^{9'}$ is suitably defined such that saturation of the alkene and combination with $\text{R}^{9'}$ gives a group of formula R^9 as defined in formula (IIA) and R^{10} is as defined in formula (IIA), followed by removal of any protecting groups; or

(h) when Y is N and Z = CR^3 , and R^{23} or R^{24} represent tetrazolyl, reacting a compound of formula IIA₁ or IIA₂

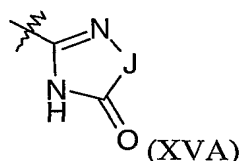
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with a compound of formula PN_3 wherein P is sodium, a trialkylsilyl, an alkyltin or ammonium gives a group of formula IIA_1 or IIA_2 wherein X^1 , R^9 , W, W' are defined in
 5 IIA; or

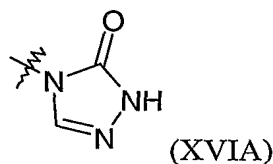
(i) when Y is N and $Z = CR^3$, and R^{23} or R^{24} represent a group of formula (XVA)



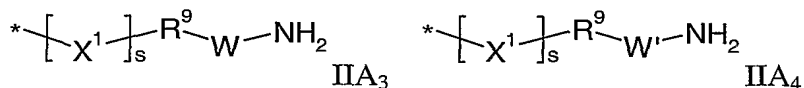
reacting a compound of formula IIA_1 or IIA_2 wherein IIA_1 or IIA_2 are as defined in (h)
 10 above with hydroxylamine, followed by treatment with 1,1'-thiocarbonyldiimidazole and subsequent treatment with silica gives a group of formula (XVA) wherein J is S, alternatively reacting a compound of formula IIA_1 or IIA_2 wherein IIA_1 or IIA_2 are as defined in (h) above with hydroxylamine, followed by treatment with a chloroformate gives a group of formula (XVA) wherein J is O; or

15

(j) when Y is N and $Z = CR^3$, and R^{23} or R^{24} represent a group of formula (XVIA)



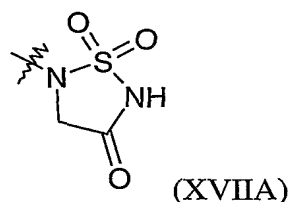
reacting a compound of formula IIA_3 or IIA_4



20 with a source of phosgene followed by treatment with formyl hydrazine and subsequent treatment with base; or

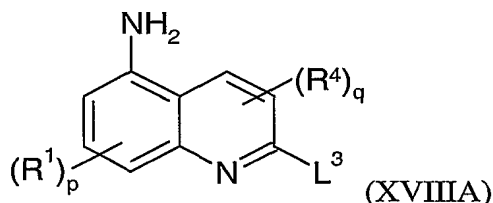
(k) when Y is N and $Z = CR^3$, and R^{23} or R^{24} represent a group of formula (XVIIA)

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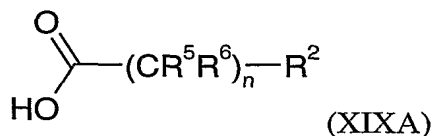


reacting a compound of formula IIA_3 or IIA_4 as defined above in (j) with ethyl
chloroacetate, followed by reaction with (chlorosulfonyl)-carbamic acid, 1,1-dimethylethyl
ester and subsequent treatment with acid and base gives the compound of formula
5 (XVIIA);

(l) when Y is N, X is NHC(O) and m is 0, compounds of the formula (VIIIa) as defined
above in (c) can be derived by reacting a compound of formula (XVIIIa)

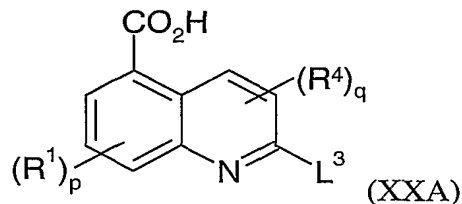


10 with a suitable acid of formula (XIXa)

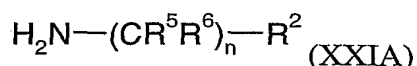


wherein L^3 is a leaving group (e.g. halogen, paratoluene sulphonate or methane
15 sulphonate), and all other variables are as defined in relation to formula (IA); or

(m) when Y is N, X is C(O)NH and m is 0, compounds of the formula (VIIIa) as defined
above in (c) can be derived by reacting a compound of formula (XXa)

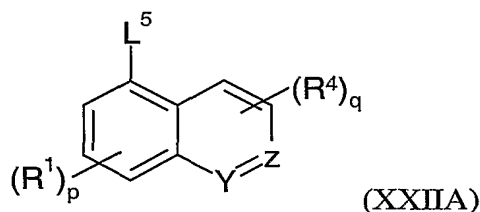


20 with a suitable amine of formula (XIXa)



wherein L^3 is a leaving group (e.g. halogen, paratoluene sulphonate or methane sulphonate), and all other variables are as defined in relation to formula (IA); or

- 5 (n) when Y is N, X is C(O)NH and m is 0, compounds of the formula (VIII A) as defined above in (c) can be derived by reacting a compound of formula (XXII A)



- 10 with a suitable amine of formula (XXIA), wherein L^5 is a halogen (e.g. bromine or iodine) and all other variables are as defined in relation to formula (IA) with a suitable source of carbon monoxide and a suitable catalyst;

and optionally after (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (m) or (n) carrying out one or more of the following:

- 15
- converting the compound obtained to a further compound of the invention
 - forming a pharmaceutically acceptable salt, prodrug or solvate of the compound.

- 20 In processes (a), (b), (l) and (m) the coupling reaction is conveniently carried out in an organic solvent such as dichloromethane, *N,N*-dimethylformamide or 1-methyl-2-pyrrolidinone.

- If L^1 or L^2 represent a hydroxyl group, it may be necessary or desirable to use a coupling agent such as bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP). If L^1 or L^2 are chloride, such compounds may be conveniently prepared by treatment of the corresponding carboxylic acid derivative under standard conditions (such as thionyl chloride in dichloromethane with additional *N,N*-dimethylformamide) and used in a solvent such as acetone or dichloromethane with a suitable base such as potassium carbonate or triethylamine.
- 25

In process (c) the reaction may be performed in an organic solvent such as acetonitrile, *N,N*-dimethylformamide or 1-methyl-2-pyrrolidinone, and in the presence of a suitable base such as sodium hydride, triethylamine or potassium carbonate at a temperature in the range from, e.g. 50°C to 150°C, in particular from 80°C to 120°C, either in a microwave or conventional thermal conditions.

In process (d), if the compound of formula (VIII A) is reacted with a compound of formula (X A), then the reaction is conveniently carried out in an organic solvent such as acetonitrile, e.g. at ambient temperature (20°C), in the presence of catalytic bistrisphenylphosphine dichloride palladium(0), copper (I) iodide and a base (e.g. triethylamine). The subsequent hydrogenation reaction may use hydrogen gas with a catalyst such as 5% rhodium on carbon in a solvent, for example, ethyl acetate or ethanol, and at a pressure of 3 bar.

Alternatively, if the compound of formula (VIII A) is reacted with a compound of formula (XIA), then it is preferred if the compound of formula (XIA) is pre-treated by reaction with a hydroborating reagent (e.g. 9-borabicyclo[3.3.1]nonane or catecholborane) in an organic solvent such as diethyl ether or tetrahydrofuran at a temperature in the range from, e.g. 0°C to 80°C, in particular from 60°C to 70°C, for about 2 to 3 hours. The pre-treated compound is then reacted with the compound of formula (VIII A) in the presence of a suitable base (e.g. sodium hydroxide or tri-potassium orthophosphate) and a palladium catalyst (e.g. dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct), typically at a temperature in the range from 25°C to 90°C, particularly from 60°C to 70°C, for about 2 to 24 hours.

In process (e), the reaction with the vinyl compound of formula (XII A) may conveniently be carried out in a solvent such as *N,N*-dimethylformamide and in the presence of catalytic dichlorobis(triphenylphosphine) palladium, at elevated temperature, e.g. at about 70°C. The subsequent addition reaction with the compound of formula (XIII A) may be performed under acidic or basic conditions, for example, in acetic acid in a solvent such as methanol or isopropanol at elevated temperature, e.g. at about 100°C.

In process (f), the reaction of the vinyl compound of formula (XVIIIa) may be performed by procedures analogous to those outlined in the previous paragraph on process (e). The subsequent oxidation reaction may be carried out under standard conditions, for example, by using ozone followed by treatment with dimethylsulfide or triphenylphosphine in a suitable solvent such as dichloromethane, or, by using osmium tetroxide and sodium periodate in a suitable solvent such as 1,4-dioxane and water. The reductive amination step may be conveniently carried out in the presence of a reducing agent such as sodium cyanoborohydride, triacetoxyborohydride or sodium borohydride, in a polar solvent such as methanol, ethanol or dichloromethane either alone or in combination with acetic acid.

In process (g), the compound of formula (XIVa) is pre-treated by reaction with a hydroborating reagent (such as 9-borabicyclo[3.3.1]nonane or catecholborane) in a solvent (such as diethyl ether or tetrahydrofuran) at a temperature in the range from 0°C to 80°C (in particular from 60°C to 70°C) for about 2 to 3 hours, then cooling the reaction mixture to room temperature and adding a solution of a base (such as sodium hydroxide in water or *tri*-potassium orthophosphate in water) followed by a solution of the compound of formula (VIIIa) in a solvent (such as *N,N*-dimethylformamide) and a palladium catalyst (such as *tetrakis*(triphenylphosphine)palladium (II)). The resulting reaction mixture is stirred at a temperature in the range from 25°C to 90°C (particularly from 60°C to 70°C) for about 2 to 24 hours to yield the desired compounds of formula (IA).

In process (h), the compound of formula IIA₁ or IIA₂ is treated with a compound of the formula PN₃ in a solvent (such as toluene, *N,N*-dimethylformamide or 1-methyl-2-pyrrolidinone) optionally in the presence of catalyst (such as dibutyltin oxide) at a temperature in the range from 70°C to 120°C.

In process (i), the compound of formula IIA₁ or IIA₂ wherein IIA₁ or IIA₂ are defined as in (h) and J = O, is treated with hydroxylamine in a suitable solvent (such as methanol or ethanol) at a temperature in the range from 70°C to 130°C. The resulting intermediate is treated with a suitable chloroformate (such as 2-ethylhexylchloroformate) in a suitable solvent (such as dichloromethane) and heated at a temperature in the range from 70°C to

150°C to give the desired compounds of the formula (IA). Alternatively, when J = S, treatment of the hydroxylamine adduct with 1,1'-thiocarbonyldiimidazole in a suitable solvent (such as tetrahydrofuran) and addition of silica yields the desired compounds of the formula (IA).

5

In process (j), the compound of formula IIA_3 or IIA_4 is treated with phosgene or a phosgene equivalent (such as triphosgene) in a suitable solvent (such as dichloromethane) with a suitable base (such as triethylamine). The resulting compound is further treated with formyl hydrazine and this subsequently with a base (such as potassium hydroxide) in a suitable solvent (such as methanol) at a temperature in the range from 50°C to 130°C to give the desired compounds of the formula (IA).

In process (k), the compound of formula IIA_3 or IIA_4 wherein IIA_3 or IIA_4 are as defined above in (j) is treated with ethyl chloroacetate in a suitable solvent (such as acetonitrile) with a suitable base (such as triethylamine) at a temperature in the range from 50°C to 130°C. Treatment of this adduct with (chlorosulfonyl)-carbamic acid, 1,1-dimethylethyl ester in a suitable solvent (such as dichloromethane) and subsequent treatment with a suitable acid (such as trifluoroacetic acid) and a suitable base (such as sodium methoxide) to give the desired compounds of the formula (IA).

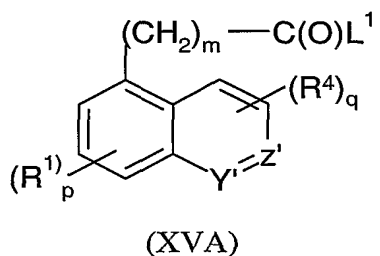
In process (n), suitable palladium catalysts include dichlorobis(triphenylphosphine)palladium(II) and the reaction may be carried out in an inert solvent such as *N*-methyl pyrrolidinone, at a temperature between 25°C and 150°C, preferably 100°C and under a 1-15 bar pressure of carbon monoxide, preferably 6 bar to give the desired compounds of the formula (VIII).

Compounds of formulae (IVA), (VA), (VIA), (VIIA), (IXA), (XA), (XIA), (XIIA), (XIIIA), (XIVA), (XIXA), (XXIA) and (XXIIA) are either commercially available, are known in the literature or may be prepared using known techniques.

30

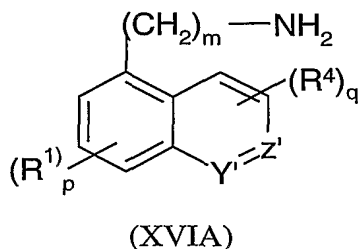
Compounds of formula (VIII A) are novel compounds and form a further aspect of the invention. Examples of preparation methods for certain of these compounds are given hereinafter in the examples. Other examples can be prepared by analogous methods. In particular, compounds of formula (VIII A) or analogues where Y is CL^3 and Z is N can be prepared by either

(i) reacting a compound of formula (XVA)



wherein L^1 represents a leaving group (e.g. hydroxyl or halogen) and R^1 , R^4 , m, p and q are as defined in formula (IA), and one of Y' or Z' is N and the other is a group CL^3 where L^3 is as defined in relation to formula (VIII A), with a compound of formula (VA) as defined above;

(ii) reacting a compound of formula (XVIA)



wherein R^1 , R^4 , m, p and q are as defined in formula (IA), Y' and Z' are as defined in relation to formula (XVA) with a compound of formula (VIIA) as defined above. Reaction conditions analogous to those described above in relation to steps (a) and (b) are suitably employed.

Compounds of formula (XVA) and (XVIA) are either commercially available, are known in the literature or may be prepared using known techniques.

5 Compounds of formula (XVIII A) are either known in the literature or may be prepared by nitration of the corresponding 2-chloroquinoline under standard conditions (such as nitric acid and sulfuric acid at a temperature in the range of 0°C to 100°C) followed by subsequent reduction to the corresponding aniline derivative under standard conditions (such as iron powder, acetic acid, hydrochloric acid, water and ethanol at a temperature in the range of 20°C to 100°C). Alternatively, a suitable nitro derivative with no substitution
10 at the 2-position may be functionalised to compounds of formula (XVIII A) by N-oxidation of the quinoline nitrogen under standard conditions (such as peracetic acid in acetic acid at a temperature in the range of 0°C to 60°C) and further conversion to its 2-chloro derivative by treatment with a suitable chlorinating agent (such as phosphorus oxychloride at a temperature in the range of 0°C to 100°C). 2-Hydroxy compounds may be similarly
15 converted to the 2-chloro derivatives by treatment with similar chlorinating agents.

Compounds of formula (XXA) may be prepared from an appropriately substituted 5-bromo-2-halo-quinoline, such as 5-bromo-2,6-dichloroquinoline, by treatment with a Grignard reagent followed carbon dioxide. Suitable Grignard reagents include
20 isopropylmagnesium chloride and the reaction may be carried out in an inert solvent such as tetrahydrofuran or diethyl ether, at a temperature from -30°C to 30°C, but preferentially at 0°C. The reaction may be poured onto solid carbon dioxide or more preferably CO₂ gas may be bubbled through the reaction mixture.

25 The appropriately substituted 5-bromo-2-halo-quinoline may be prepared by bromination of an appropriately substituted 2-haloquinoline such as 2,6-dichloroquinoline. The reaction may be carried by treatment with bromine in the presence of a Lewis acid such as aluminium trichloride at temperatures between -10°C to 150°C, preferably at 120°C, in the absence of solvent.

30

Compounds of formula (VIII A) where Y is N and Z is C-L₃, where L₃ is a leaving group such as halogen, R¹, R⁴, p and q are as defined in formula (IA) and m is 0, may be

prepared from an appropriately substituted 5-bromo-quinoline by treatment with an amine of formula (XXIA), where R^5 , R^6 , n and R^2 are as defined in formula (IA), in the presence of carbon monoxide and a palladium catalyst, followed by introduction of the 2-chlorine by treatment with an oxidising agent then a chlorinating agent. Suitable palladium catalysts include dichlorobis(triphenylphosphine)palladium (II) and the reaction may be carried out in an inert solvent such as N-methyl pyrrolidinone, at a temperature between 25°C and 150°C, preferably 100°C and under a 1-15 bar pressure of carbon monoxide, preferably 6 bar. The 2-chlorine may be introduced by treatment with an oxidant such as hydrogen peroxide in a solvent such as acetic acid at 65°C followed by treatment with a chlorinating agent such as thionyl chloride or preferably phosphorous oxychloride at a temperature of 120°C.

The appropriately substituted 5-bromo-quinolines may be prepared by literature methods (J Heterocyclic Chem., 1967, 4, 410, Khimiya Geterotsiklicheskikh Soedinenii, 1988, 8, 1084).

Compounds of formula (IA) can be converted into further compounds of formula (IA) using standard procedures. For example, compounds of formula (IA) in which R^2 represents a halogen atom may be converted to a corresponding compound of formula (IA) in which R^2 represents a C_1 - C_6 alkyl group by reaction with an alkyl Grignard reagent (e.g. methyl magnesium bromide) in the presence of a catalyst such as [1,3-bis(diphenylphosphino)propane]dichloronickel (II) in a solvent such as tetrahydrofuran.

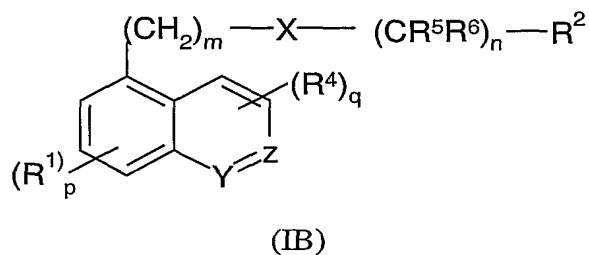
In a further example of the conversion of a compound of formula (IA) to another compound of formula (IA); a compound of formula (IA) where the group $NR^{13}R^{14}$ represents NH_2 may be converted into another compound of formula (IA) wherein R^{13} represents H and R^{14} is as defined in formula (IIIA), by treatment with an appropriate aldehyde (for example a suitably protected hydroxyl-acetaldehyde) in a reductive amination reaction. Suitable reducing agents include sodium cyanoborohydride, triacetoxyborohydride or sodium borohydride and the reaction may be carried out in a

polar solvent such as methanol, ethanol or dichloromethane either alone or in combination with acetic acid.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (IA) above may involve, at various stages, the addition and removal of one or more protecting groups. The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

The compounds of formula (IA) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate, or an alkali metal salt such as a sodium or potassium salt. Other pharmaceutically acceptable salts, as well as prodrugs such as pharmaceutically acceptable esters and pharmaceutically acceptable amides may be prepared using conventional methods.

In a further aspect the invention provides a compound of formula (IB)



25 or a pharmaceutically acceptable salt, prodrug or solvate thereof,

wherein p is 0, 1 or 2;

each R¹ is independently selected from halogen, or optionally substituted C₁₋₆ alkyl,

m is 0, 1, 2 or 3;

X is C(O)NH or NHC(O);

n is 0, 1, 2 or 3;

each R^5 and each R^6 are independently selected from hydrogen or C_{1-3} alkyl, or R^5 and R^6 together with the carbon atom to which they are both attached forms a C_{3-6} cycloalkyl ring, R^2 is an optionally substituted cycloalkyl group;

- 5 one of Y or Z is nitrogen and the other is a group CR^3 where R^3 is hydrogen, or a group R^7 , OR^7 , SR^7 , NR^7R^8 , where R^7 and R^8 are independently selected from hydrogen, optionally substituted C_{1-10} alkyl, an optionally substituted cycloalkyl or an optionally substituted heterocyclic group, or R^7 and R^8 together with the nitrogen to which they are attached form an optionally substituted heterocyclic ring which may contain additional heteroatoms, and
10 may further comprise bridging groups;

q is 0, 1 or 2,

and each R^4 is independently selected from halogen or optionally substituted C_{1-6} alkyl, with the proviso that where p is 0, q is 0, m is 0, n is 0, X is $NHC(O)$, Y is nitrogen, Z is CR^3 and R^3 is methyl, R^2 is not a cyclopropyl group

15

Certain compounds of formula (IB) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (IB) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

20

For the avoidance of doubt, it is hereby noted that the numbering and definition of groups and substituents provided herein in respect of formula (IB) is distinct and separate from that provided herein above in respect of formula (IA).

- 25 In an embodiment of the invention, in formula (IB) Y is nitrogen and Z is a group CR_3 .

In an embodiment of the invention, in formula (IB) p is 0 or 1. Where p is 1, R^1 is preferably arranged ortho to group $-(CH_2)_mX(CH_2)_nR^2$ on the ring.

- 30 Preferred groups R^1 in formula (IB) include halogen, such as chloro, fluoro or C_1-C_6 alkyl such as methyl, optionally substituted by a substituent selected from hydroxyl, halogen and C_1-C_6 alkoxy. Preferably R^1 is chloro or methyl.

In an embodiment of the invention, in formula (IB) m is 0 or 1 and preferably m is 0.

In an embodiment of the invention, in formula (IB) n is 0, 1 or 2, and preferably n is 1.

5

In formula (IB), where R^5 and R^6 together with the carbon atom to which they are both attached forms a cycloalkyl ring, it is preferably a cyclopropyl ring.

In an embodiment of the invention, in formula (IB) each R^5 and R^6 is hydrogen.

10

In an embodiment of the invention, in formula (IB) R^2 represents a C_{3-8} cycloalkyl group, more preferably a C_{5-7} cycloalkyl ring, e.g. a C_5 or C_6 cycloalkyl ring. Most preferably R^2 is an optionally substituted cyclohexyl ring.

15 Optional substituents for the ring R^2 in formula (IB) include one or more groups selected from halogen, halo C_{1-6} alkyl, C_{1-6} alkyl or $S(O)_f R^{50}$, where f is 0, 1 or 2 and R^{50} is C_{1-6} alkyl. In particular, R^2 may carry one or two substituents which are in particular, fluoro, methyl or trifluoromethyl.

20 In formula (IB), where R^2 is cyclohexyl, substituents where present are preferably situated at the 1 and/or 4 positions of the ring.

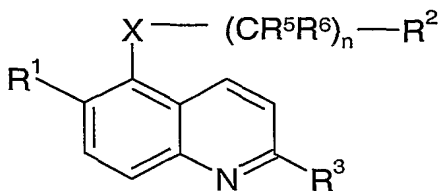
Preferred optional substituents for C_{1-6} alkyl groups R^4 in formula (IB) include halogen, hydroxy and C_{1-6} alkoxy, such as methoxy.

25

In an embodiment of the invention, in formula (IB) q is 0.

In an embodiment of the invention, the compounds of formula (IB) are selected from compounds of formula (IIIB)

40



(III)

where R^1 , X , R^5 , R^6 , n , R^2 and R^3 are as defined above with respect to formula (IB).

In an embodiment of the invention, in formula (IB) R^3 is a group R^7 , OR^7 , SR^7 , NR^7R^8 ,
 5 where R^7 and R^8 are as defined above with respect to formula (IB).

In an embodiment of the invention, in formula (IB) where R^7 and R^8 includes bridging groups, these preferably form a fused 5/6 membered ring system, for example a
 10 diazabicyclo[2.2.1]hept-2-yl group.

In formula (IB), optional substituents for C_{1-10} alkyl groups R^7 and R^8 , include halogen, nitro, cyano, OR^{13} , $OC(O)R^{13}$, $C(O)OR^{13}$, $C(O)NR^{13}$, SR^{13} , $S(O)R^{13}$, $S(O_2)R^{13}$, $NR^{13}R^{14}$, -
 $NR^{13}C(O)-$, $-NR^{13}S(O)_rR^{14}$, $-S(O)_rNR^{13}R^{14}$, $NR^{15}C(O)NR^{13}R^{14}$, or

15

$NR^{13}C(O)NR^{14}S(O)_rR^{15}$, optionally substituted cycloalkyl, optionally substituted aryl,
 optionally substituted aryloxy or optionally substituted heterocyclic groups, where r is 0, 1
 or 2, and preferably 2, and R^{13} , R^{14} and R^{15} are independently selected from hydrogen or
 C_{1-7} alkyl, aryl, cycloalkyl or a heterocyclic group, any of which may be optionally
 substituted, and where appropriate, R^{13} and R^{14} together with the nitrogen atom to which
 they are attached may form an optionally substituted heterocyclic ring, which may contain
 20 additional heteroatoms.

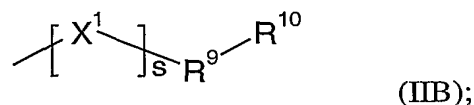
In formula (IB), optional substituents for cycloalkyl or heterocyclic groups R^7 and R^8 , as
 well as for rings formed by R^7 and R^8 include those groups listed above for C_{1-10} alkyl
 groups, as well as alkyl substituted by any of said groups, and in particular by groups of
 25 formula $-(CH_2)_dR^{30}$ where d is 1 to 10, and preferably 1-6 and R^{30} is halogen, nitro, cyano,
 OR^{13} , $OC(O)R^{13}$, $C(O)OR^{13}$, $C(O)NR^{13}$, SR^{13} , $S(O)R^{13}$, $S(O_2)R^{13}$, $NR^{13}R^{14}$, $-NR^{13}C(O)-$,
 $-NR^{13}S(O)_rR^{14}$, $-S(O)_rNR^{13}R^{14}$, $NR^{15}C(O)NR^{13}R^{14}$, or $NR^{13}C(O)NR^{14}S(O)_rR^{15}$ where r is
 0, 1 or 2, where R^{13} , R^{14} and R^{15} are as defined above. A particular group R^{30} is $NR^{13}R^{14}$.

- In formula (IB), optional substituents for alkyl groups R^{13} , R^{14} and R^{15} include halogen, nitro, cyano, OR^{16} , $OC(O)R^{16}$, $C(O)OR^{16}$, SR^{16} , $S(O)R^{16}$, $S(O_2)R^{16}$, $NR^{16}R^{17}$, $-NR^{16}C(O)-$, $-NR^{16}S(O)_rR^{17}$, $-S(O)_rNR^{16}R^{17}$, $NR^{18}C(O)NR^{16}R^{17}$, or $NR^{16}C(O)NR^{17}S(O)_rR^{18}$ where R^{16} , R^{17} and R^{18} are independently selected from hydrogen or C_{1-7} alkyl, aryl, cycloalkyl or heterocyclic groups, or where appropriate, R^{16} and R^{17} together with the nitrogen atom to which they are attached form a heterocyclic group, which optionally contains further heteroatoms.
- 10 In formula (IB), where R^{13} , R^{14} and R^{15} are aryl, cycloalkyl or heterocyclic groups, or where R^{13} and R^{14} together with the nitrogen atom to which they are attached form a heterocyclic group, they may be optionally substituted by a groups $-(CH_2)_eR^{31}$ where e is 0 or an integer of from 1 to 10, preferably from 1-6, and R^{31} is halogen, nitro, cyano, OR^{16} , $OC(O)R^{16}$, $C(O)OR^{16}$, $C(O)NR^{16}$, SR^{16} , $S(O)R^{16}$, $S(O_2)R^{16}$, $NR^{16}R^{17}$, $-NR^{16}C(O)-$, $-NR^{16}S(O)_rR^{17}$, $-S(O)_rNR^{16}R^{17}$, $NR^{18}C(O)NR^{16}R^{17}$, or $NR^{16}C(O)NR^{17}S(O)_rR^{18}$, cycloalkyl, aryl, aryloxy or heterocyclic groups, where r is as defined above, and R^{16} , R^{17} and R^{18} are as defined above. A particular group for R^{31} is $NR^{16}R^{17}$.

- 20 In an embodiment of the invention, in formula (IB) preferred substituents for R^7 or R^8 include halogen, hydroxy and C_{1-6} alkoxy.

In formula (IB), suitable substituents for aryl groups R^{13} , R^{14} or R^{15} include halogen, hydroxy or C_{1-6} alkylsulphonylamino.

- 25 In formula (IB), preferred examples of R^3 include groups of formula (IIB)



where X^1 represents an oxygen or sulphur atom or a group $>N-R^{11}$ and R^{11} is hydrogen or a C_{1-5} alkyl group which may be optionally substituted by one or more substituents selected from hydroxy, halogen or C_{1-6} alkoxy;

- 30 s is 0 or 1;

R^9 represents a bond or a C_1 - C_5 alkylene group, which may be optionally substituted,

R^{10} represents hydrogen, hydroxyl, carboxy, a group $-NR^{19}R^{20}$, an optionally substituted carbocyclic or an optionally substituted heterocyclic ring, either or which may include bridging groups,

where R^{19} and R^{20} are independently selected from hydrogen, pyrrolidine, piperazine,

- 5 piperidine, C_{1-6} alkylcarbonyl, C_{2-7} alkenyl, optionally substituted C_{1-7} alkyl, or $C(O)NHS(O_2)R^{21}$ where R^{21} is C_{1-5} alkyl, provided that when s is 1 and R^9 is a bond, R^{10} is other than hydroxy, carboxy or a group $-NR^{19}R^{20}$.

- In formula (IIB), optional substituents for C_{1-7} alkyl groups R^{19} and R^{20} include at least
 10 one substituent selected from halogen, carboxyl, hydroxyl, C_1-C_6 alkylamino, di- C_1-C_6 alkylamino, $-NH(CH_2)_{2-4}OH$, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 alkoxy carbonyl, $-NR^{37}R^{38}$ and $-CONR^{38}R^{37}$, $-NR^{37}COR^{38}$ and an optionally substituted saturated or unsaturated 3- to 10-membered ring system which may comprise at least one ring heteroatom selected from nitrogen, oxygen and sulphur; where R^{37} and R^{38} are
 15 independently selected from hydrogen atom or a C_1-C_6 alkyl, C_2-C_6 hydroxyalkyl or C_3-C_8 cycloalkyl group, or R^{37} and R^{38} together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic ring;

- In formula (IIB), where R^{19} and R^{20} carries a substituent which is a ring system as
 20 described above, this is suitably optionally substituted by at least one substituent selected from halogen, hydroxyl, oxo, carboxyl, cyano, C_1-C_6 alkyl, C_1-C_6 hydroxyalkyl, $-(CH_2)_tNR^{22}R^{23}$, $-(CH_2)_tCONR^{24}R^{25}$, $-(CH_2)_tNR^{26}COR^{27}$, or $-(CH_2)_tR^{29}$ where R^{22} and R^{23} each independently represent a hydrogen atom or a C_1-C_6 alkyl, C_2-C_6 hydroxyalkyl or C_3-C_8 cycloalkyl group, or R^{22} and R^{23} together with the nitrogen atom to which they
 25 are attached form a 3- to 8-membered saturated heterocyclic ring;
 R^{24} and R^{25} each independently represent a hydrogen atom or a C_1-C_6 alkyl, C_2-C_6 hydroxyalkyl or C_3-C_8 cycloalkyl group, or R^{24} and R^{25} together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic ring;
 R^{26} and R^{27} each independently represent a hydrogen atom or a C_1-C_6 alkyl,
 30 C_2-C_6 hydroxyalkyl or C_3-C_8 cycloalkyl group;
 R^{29} is aryl such as phenyl, and
 t is 0, 1, 2, 3, 4, 5 or 6.

In formula (IIB), where R^{10} is an optionally substituted carbocyclic or an optionally substituted heterocyclic ring, suitable substituents include those listed above for ring substituents on R^{19} and R^{20} as described in the paragraph above.

5

In formula (IIB), optional substituents for C_{1-5} alkylene groups R^9 include one or more substituents selected from hydroxyl, halogen, C_1-C_6 alkoxy, C_1-C_6 alkylthio, C_1-C_6 hydroxyalkyl, C_1-C_6 hydroxyalkyloxy, C_1-C_6 alkoxycarbonyl, C_3-C_8 cycloalkyl, phenyl (optionally substituted by at least one substituent selected from halogen, hydroxyl and C_1-C_6 alkylsulphonylamino), benzyl, indolyl (optionally substituted by at least one substituent selected from C_1-C_6 alkoxy), oxopyrrolidinyl, phenoxy, benzodioxolyl, phenoxyphenyl, piperidinyl and benzyloxy.

In formula (IIB), any hydroxyl groups will not normally be attached to a carbon atom adjacent a nitrogen atom. Further, when R^9 is other than a bond, the group R^{10} may be attached to the C_1-C_5 alkyl moiety of R^9 at any suitable point; thus R^{10} may be attached to an internal or terminal carbon atom of the C_1-C_5 alkyl moiety of R^9 .

In formula (IIB), R^{11} represents a hydrogen atom or a C_1-C_5 alkyl group which may be optionally substituted by at least one substituent (e.g. one, two or three substituents independently) selected from hydroxyl, halogen (e.g. fluorine, chlorine, bromine or iodine) and C_1-C_6 , or C_1-C_4 , alkoxy.

In an embodiment of the invention, in formula (IIB) R^{11} represents a hydrogen atom or a C_1-C_5 alkyl group which may be optionally substituted by at least one hydroxyl group.

In formula (IIB), s is preferably 0.

In an embodiment of the invention, in formula (IIB) where s is 0, R^9 is a C_{1-5} alkylene group such as methylene, and R^{10} is a heterocyclic group such as a saturated nitrogen containing ring, for instance piperidine. In an alternative embodiment, in formula (IIB) s is 1 and X^1 is a group $>NR^{11}$ where R^{11} is hydrogen or a C_{1-5} alkyl group such as methyl.

In formula (IIB), preferred groups R⁹ include a bond or a C₁-C₅ alkyl group which may be optionally substituted by at least one substituent (e.g. one, two or three substituents independently) selected from hydroxyl, halogen (e.g. fluorine, chlorine, bromine or iodine), C₁-C₆, or C₁-C₄, alkoxy, C₁-C₆, or C₁-C₄, alkylthio, C₁-C₆, or C₁-C₄, hydroxyalkyl, C₁-C₆, or C₁-C₄, hydroxyalkyloxy, C₁-C₆, or C₁-C₄, alkoxycarbonyl, C₃-C₈ cycloalkyl, phenyl (optionally substituted by at least one substituent, e.g. one, two or three substituents independently, selected from halogen, hydroxyl and C₁-C₆, or C₁-C₄, alkylsulphonylamino), benzyl, indolyl (optionally substituted by at least one substituent, e.g. one, two or three substituents independently, selected from C₁-C₆, or C₁-C₄, alkoxy), oxopyrrolidinyl, phenoxy, 1,3-benzodioxolyl, phenoxyphenyl, piperidinyl and benzyloxy.

In an embodiment of the invention, in formula (IIB) R⁹ represents a bond or a C₁-C₄ alkyl group which may be optionally substituted by one, two or three substituents independently selected from hydroxyl, C₁-C₂ alkoxy, methylthio, C₁-C₂ hydroxyalkyl, C₁-C₂ hydroxyalkyloxy, methoxycarbonyl, C₃-C₆ cycloalkyl, phenyl (optionally substituted by at least one substituent selected from halogen, hydroxyl and methylsulphonylamino), benzyl, indolyl (optionally substituted by at least one methoxy), oxopyrrolidinyl, phenoxy, benzodioxolyl, phenoxyphenyl, piperidinyl and benzyloxy.

In another embodiment of the invention, in formula (IIB) R⁹ represents a bond or a C₁-C₄ alkyl group which may be optionally substituted by one, two or three substituents independently selected from hydroxyl, C₁-C₂ alkoxy, methylthio, C₁-C₂ hydroxyalkyl, C₁-C₂ hydroxyalkyloxy, methoxycarbonyl, cyclopropyl, phenyl (optionally substituted by at least one substituent selected from chlorine, hydroxyl and methylsulphonylamino), benzyl, indolyl (optionally substituted by at least one methoxy), oxopyrrolidinyl, phenoxy, benzodioxolyl, phenoxyphenyl, piperidinyl and benzyloxy.

In a preferred embodiment of the invention, in formula (IIB) R⁹ represents a bond or a C₁-C₄ alkyl group which is unsubstituted.

In an embodiment of the invention, in formula (IIB) R^{10} represents hydrogen, hydroxyl, carboxy or a group $-NR^{19}R^{20}$.

In formula (IIB), preferably R^{19} and R^{20} each independently represent hydrogen,
 5 pyrrolidinyl, C_1 - C_6 , or C_1 - C_4 , alkylcarbonyl, C_2 - C_7 alkenyl, or C_1 - C_7 alkyl optionally substituted with at least one substituent (e.g. one, two, three or four substituents independently) selected from carboxyl, hydroxyl, $NR^{45}R^{46}$, OR^{45} , SR^{45} , $OC(O)R^{45}$ and $C(O)OR^{45}$ (where R^{45} and R^{46} are independently selected from hydrogen or C_{1-6} alkyl, and preferably C_{1-4} alkyl,) and a saturated or unsaturated 3- to 10-membered ring system which
 10 may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted by at least one substituent (e.g. one, two, three or four substituents independently) selected from halogen (e.g. fluorine, chlorine, bromine or iodine), hydroxyl, oxo, carboxyl, cyano, C_1 - C_6 , or C_1 - C_4 , alkyl, C_1 - C_6 , or C_1 - C_4 , hydroxyalkyl,
 15 $-NR^{22}R^{23}$, $-(CH_2)_tNR^{24}R^{25}$ and $-CONR^{26}R^{27}$, where R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} and t are as defined above.

For instance, in formula (IIB) R^{19} and R^{20} each independently represent hydrogen, pyrrolidinyl, C_1 - C_2 alkylcarbonyl, C_5 - C_7 alkenyl, or C_1 - C_7 alkyl optionally substituted
 20 with one or two substituents independently selected from carboxyl, hydroxyl, amino, C_1 - C_2 alkylamino, di- C_1 - C_2 alkylamino, $-NH(CH_2)_{2-4}OH$, C_1 - C_2 alkoxy, C_1 - C_2 alkylthio, C_1 - C_2 alkoxy carbonyl, and a saturated or unsaturated 3- to 10-membered ring system which may comprise at least one ring heteroatom (e.g. one, two, three or four ring heteroatoms independently) selected from nitrogen, oxygen and sulphur, the ring system
 25 being optionally substituted by at least one substituent (e.g. one, two, three or four substituents independently) selected from fluorine, hydroxyl, oxo, carboxyl, cyano, C_1 - C_2 alkyl, C_1 - C_2 hydroxyalkyl, $-NR^{22}R^{23}$, $-(CH_2)_tNR^{24}R^{25}$ and $-CONR^{26}R^{27}$ where R^{22} , R^{23} , R^{24} , R^{25} , R^{26} , R^{27} and t are as defined above.

30 Specific examples of R^{19} and R^{20} in formula (IIB) include hydrogen, pyrrolidinyl, methylcarbonyl, C_7 alkenyl, or C_1 - C_7 alkyl optionally substituted with one or two substituents independently selected from carboxyl, hydroxyl, methylamino,

di-methylamino, $-\text{NH}(\text{CH}_2)_2\text{OH}$, methylthio, $\text{C}_1\text{-C}_2$ alkoxycarbonyl, and a saturated or unsaturated 3- to 10-membered ring system which may comprise one, two or three ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted by one or two substituents independently selected from
 5 fluorine, hydroxyl, oxo, $\text{C}_1\text{-C}_2$ alkyl and hydroxymethyl.

The saturated or unsaturated 3- to 10-membered ring system defined above in respect of R^{19} and R^{20} in formula (IIB), may be monocyclic or polycyclic (e.g. bicyclic) and may have alicyclic or aromatic properties. An unsaturated ring system will be partially or fully
 10 unsaturated. Examples of ring systems that may be used include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, bicyclo[2.2.1]hept-2-yl, bicyclo[2.2.1]hept-5-en-2-yl, homopiperazinyl, phenyl, 3,4-dihydro-2*H*-pyranyl, pyrrolidinyl, piperidinyl, piperazinyl, phenyl, pyrazolyl, thiazolidinyl, indanyl, thienyl, isoxazolyl, thiadiazolyl, pyrrolyl, furyl, thiazolyl, indolyl, imidazolyl, benzimidazolyl,
 15 triazolyl, tetrazolyl and pyridinyl.

In one aspect of the invention, the saturated or unsaturated 3- to 10-membered ring system of R^{19} and R^{20} in formula (IIB) is selected from cyclopropyl, cyclohexenyl, phenyl, thienyl, pyridinyl, furyl, bicyclo[2.2.1]hept-5-en-2-yl, 3,4-dihydro-2*H*-pyranyl,
 20 thiazolyl, pyrrolyl, pyrazolyl, imidazolyl and thiadiazolyl.

In formula (IIB), where R^{10} is an optionally substituted carbocyclic or heterocyclic ring, it is preferably a saturated or unsaturated 4- to 9-membered ring system which is optionally substituted.

25

Optional substituents for where R^{10} in formula (IIB) is an optionally substituted carbocyclic or heterocyclic ring, include those listed above for ring substituents on R^{19} and R^{20} i.e. at least one substituent selected from halogen, hydroxyl, oxo, carboxyl, cyano,
 30 $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ hydroxyalkyl, $-(\text{CH}_2)_t\text{NR}^{22}\text{R}^{23}$, $-(\text{CH}_2)_t\text{CONR}^{24}\text{R}^{25}$, $-(\text{CH}_2)_t\text{NR}^{26}\text{COR}^{27}$ or $-(\text{CH}_2)_t\text{R}^{29}$ where R^{22} and R^{23} each independently represent a hydrogen atom or a $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ hydroxyalkyl or $\text{C}_3\text{-C}_8$ cycloalkyl group, or R^{22}

and R²³ together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic ring;

R²⁴ and R²⁵ each independently represent a hydrogen atom or a C₁-C₆ alkyl, C₂-C₆ hydroxyalkyl or C₃-C₈ cycloalkyl group, or R²⁴ and R²⁵ together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic ring;

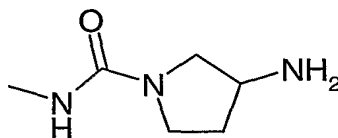
R²⁶ and R²⁷ each independently represent a hydrogen atom or a C₁-C₆ alkyl, C₂-C₆ hydroxyalkyl or C₃-C₈ cycloalkyl group;

R²⁹ is aryl such as phenyl; and

t is 0, 1, 2, 3, 4, 5 or 6.

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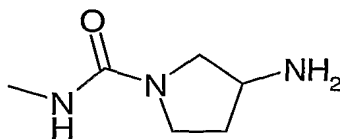
Preferred optional substituents for R¹⁰ in formula (IIB) include one or more groups selected from, amino, C₁-C₆ alkyl, C₁-C₆ alkylamino, -NH(CH₂)₂OH, -NH(CH₂)₃OH,



C₁-C₆ hydroxyalkyl, benzyl and

15

In formula (IIB) preferred rings R¹⁰ are saturated or unsaturated 4- to 9-membered ring systems which may comprise one or two ring heteroatoms independently selected from nitrogen, oxygen and sulphur, the ring system being optionally substituted by at least one substituent (e.g. one, two, three or four substituents independently) selected from hydroxyl, amino (-NH₂), C₁-C₂ alkyl, C₁-C₂ alkylamino, -NH(CH₂)₂OH, -NH(CH₂)₃OH, C₁-C₂



20

hydroxyalkyl, benzyl and

In formula (IIB), when R¹⁰ represents a saturated or unsaturated 4- to 9-membered ring system, the ring system may be monocyclic or polycyclic (e.g. bicyclic) and may have alicyclic or aromatic properties. An unsaturated ring system will be partially or fully

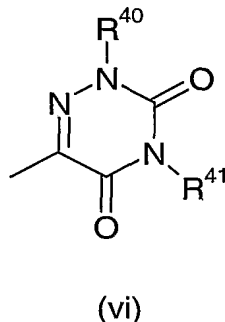
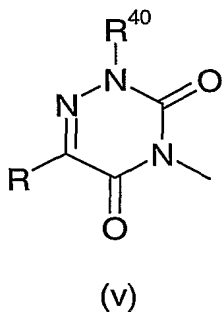
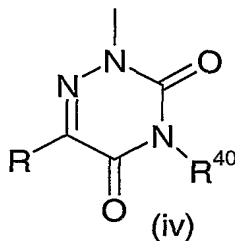
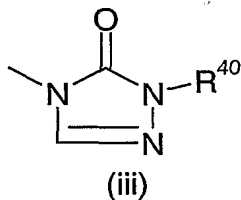
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unsaturated. Examples of ring systems that may be used include cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, bicyclo[2.2.1]hept-2-yl, bicyclo[2.2.1]hept-5-en-2-yl, 2,3-dihydro-1*H*-indenyl, homopiperazinyl, phenyl, pyrrolidinyl, piperidinyl, piperazinyl, pyrazolyl, thiazolidinyl, indanyl, thienyl,

isoxazolyl, thiadiazolyl, pyrrolyl, furyl, thiazolyl, indolyl, imidazolyl, benzimidazolyl, triazolyl, tetrazolyl and pyridinyl.

In one embodiment of the invention, in formula (IIB) the saturated or unsaturated 4- to 9-membered ring system R^{10} is selected from cyclobutyl, cyclohexyl, bicyclo[2.2.1]hept-2-yl, 2,3-dihydro-1*H*-indenyl, pyrrolidinyl, piperidinyl and piperazinyl.

Particular examples of heterocyclic rings R^{10} in formula (IIB) are groups of formula $NR^{33}R^{34}$ where R^{33} and R^{34} together with the nitrogen atom to which they are attached forms a C_{4-9} heterocyclic ring which may contain additional heteroatoms and which may be optionally substituted, and may optionally contain bridging groups. Examples of such groups R^{10} in formula (IIB) are groups of formula (iii), (iv), (v) and (vi)



where R^{40} and R^{41} are hydrogen or substituent groups as defined herein, and in particular are independently selected from hydrogen and C_{1-6} alkyl.

In formula (IIB), when R^{10} is a group $NR^{33}R^{34}$, it is preferably a saturated five or six-membered heterocyclic ring which may comprise a second ring heteroatom selected from nitrogen and oxygen. The ring is optionally substituted for example with at least one substituent selected from those listed above for ring substituents on R^{19} and R^{20} .

Particular substituents however include hydroxyl, halogen, C₁-C₆ alkyl, amino, mono or di-C₁₋₄alkylamino and hydroxyC₁-C₆alkyl.

In another embodiment of the invention, when R¹⁰ in formula (IIB) is NR³³R³⁴, R³³ and R³⁴ together with the nitrogen atom to which they are attached may form a saturated five or six-membered heterocyclic ring which may comprise a second ring heteroatom selected from nitrogen and oxygen, and may further comprise bridging groups; the ring being optionally substituted by at least one substituent (e.g. one, two, three or four substituents independently) selected from hydroxyl, amino, mono- or di-C₁₋₄alkylamino, hydroxyC₁₋₃alkylamino, halogen (e.g. fluorine, chlorine, bromine or iodine), C₁-C₆, or C₁-C₄, alkyl and C₁-C₆, or C₁-C₄, hydroxyalkyl. Examples of heterocyclic rings that may be formed include piperidinyl, piperazinyl and morpholinyl.

Where in formula (IIB) is R¹⁰ is a group NR³³R³⁴ wherein R³³ and R³⁴ together with the nitrogen atom to which they are attached may form a saturated five or six-membered heterocyclic ring which includes bridging groups, these preferably form a fused 5/6 membered ring system such as a diazabicyclo[2.2.1]hept-2-yl group.

For instance, where in formula (IIB) is R¹⁰ is a group NR³³R³⁴, R³³ and R³⁴ together with the nitrogen atom to which they are attached may form a saturated five or six-membered heterocyclic ring which may comprise a second ring heteroatom selected from nitrogen and oxygen, the ring being optionally substituted by one or two substituents independently selected from , amino, hydroxy, hydroxyC₁₋₃alkylamino, C₁-C₂ alkyl and C₁-C₂ hydroxyalkyl.

In a preferred embodiment of the invention, in formula (IIB) where s is 0, R⁹ is a bond and R¹⁰ is a group NR³³R³⁴ where R³³ and R³⁴ together with the nitrogen atom to which they are attached form a saturated five or six-membered heterocyclic ring optionally substituted as described above.

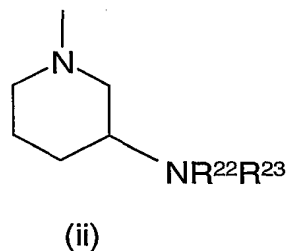
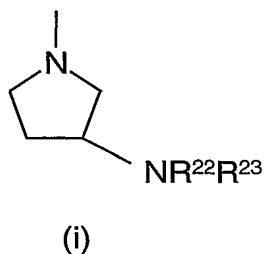
In formula (IB), preferred R²² and R²³ groups are independently hydrogen atom or a C₁-C₆, or C₁-C₄, alkyl, C₂-C₆, or C₂-C₄, hydroxyalkyl or C₃-C₈, or C₅-C₆, cycloalkyl group, or

R^{22} and R^{23} together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic ring (e.g. pyrrolidinyl or piperidinyl).

In formula (IIB), R^{24} and R^{25} preferably each independently represent a hydrogen atom or a C₁-C₆, or C₁-C₄, alkyl, C₂-C₆, or C₂-C₄, hydroxyalkyl or C₃-C₈, or C₅-C₆, cycloalkyl group, or R^{24} and R^{25} together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic ring (e.g. pyrrolidinyl or piperidinyl).

In formula (IIB), R^{26} and R^{27} each independently represent a hydrogen atom or a C₁-C₆, or C₁-C₄, alkyl, C₂-C₆, or C₂-C₄, hydroxyalkyl or C₃-C₈, or C₅-C₆, cycloalkyl group, or R^{26} and R^{27} together with the nitrogen atom to which they are attached form a 3- to 8-membered saturated heterocyclic ring (e.g. pyrrolidinyl or piperidinyl).

In a preferred embodiment of the present invention, R^3 in formula (IB) is a group of sub-formula (ii) or (ii)



Particular compounds of the present invention according to formula (IB) are as follows:

- 20 *N*-[6-Chloro-2-(4-piperidinylmethyl)-5-quinolinyl]-cyclohexaneacetamide, dihydrochloride;
N-[6-Chloro-2-(1-piperazinyl)-5-quinolinyl]-cyclohexaneacetamide, dihydrochloride;
N-[6-Chloro-2-[methyl[3-(methylamino)propyl]amino]-5-quinolinyl]-cyclohexaneacetamide, dihydrochloride;
 25 6-Chloro-*N*-(cyclohexylmethyl)-2-methyl-5-quinolinecarboxamide, hydrochloride;
N-[6-Chloro-2-[(3-hydroxypropyl)amino]-5-quinolinyl]-cyclohexaneacetamide, hydrochloride;
N-[6-Chloro-2-[(2*R*)-2,3-dihydroxypropyl]amino]-5-quinolinyl]-cyclohexaneacetamide;

- 4-[[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]amino]-butanoic acid;
N-[6-Chloro-2-[methyl[3-(methylamino)propyl]amino]-5-quinolinyl]-4-(trifluoromethyl)-
cyclohexaneacetamide, dihydrochloride;
N-[6-Chloro-2-(1-piperazinyl)-5-quinolinyl]-4-(trifluoromethyl)-cyclohexaneacetamide;
5 *N*-[6-Chloro-2-(hexahydro-1*H*-1,4-diazepin-1-yl)-5-quinolinyl]-cyclohexaneacetamide;
N-[6-Chloro-2-[(*cis*-3,5-dimethyl-1-piperazinyl)-5-quinolinyl]-cyclohexaneacetamide;
N-[6-Chloro-2-(4-methyl-1-piperazinyl)-5-quinolinyl]-cyclohexaneacetamide,
dihydrochloride;
N-[6-Chloro-2-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-5-quinolinyl]-
10 cyclohexaneacetamide, acetate;
N-[6-Chloro-2-[(3*R*)-3-pyrrolidinylamino]-5-quinolinyl]-cyclohexaneacetamide,
dihydrochloride;
N-[2-[3-(Ethylamino)propyl]-6-methyl-5-quinolinyl]-cyclohexaneacetamide,
dihydrochloride;
15 *N*-[6-Chloro-2-[3-(ethylamino)propyl]-5-quinolinyl]-cyclohexaneacetamide,
dihydrochloride;
N-[6-Chloro-2-[[2-[(2-hydroxyethyl)amino]ethyl]amino]-5-quinolinyl]-
cyclohexaneacetamide, dihydrochloride;
N-5-Quinolinyl-cyclohexaneacetamide;
20 1-Methyl-*N*-5-quinolinyl-cyclohexaneacetamide;
4-Methyl-*N*-5-quinolinyl-cyclohexaneacetamide;
N-5-Quinolinyl-cyclopentanepropanamide;
N-[6-Chloro-2-[3-[(3-hydroxypropyl)amino]propyl]-5-quinolinyl]-cyclohexaneacetamide;
N-[2-(3-Aminopropyl)-6-chloro-5-quinolinyl]-cyclohexaneacetamide;
25 *N*-[6-Chloro-2-[3-[[[(methylsulfonyl)amino]carbonyl]amino]propyl]-5-quinolinyl]-
cyclohexaneacetamide;
N-[2-[3-(Butylamino)propyl]-6-chloro-5-quinolinyl]-cyclohexaneacetamide
dihydrochloride ;
N-[6-Chloro-2-[methyl[3-(methylamino)propyl]amino]-5-quinolinyl]-1-cyclohexyl-
30 cyclopropanecarboxamide, hydrochloride;
N-[6-Chloro-2-(1-piperazinyl)-5-quinolinyl]-1-cyclohexyl-cyclopropanecarboxamide;
N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide;

N-[6-Chloro-2-[(3*S*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide;
N-[2-[(3*R*)-3-Amino-1-pyrrolidinyl]-6-chloro-5-quinolinyl]-cyclohexaneacetamide;
N-[2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-chloro-5-quinolinyl]-cyclohexaneacetamide;
N-[2-(4-Amino-1-piperidinyl)-6-chloro-5-quinolinyl]-cyclohexaneacetamide;
5 *N*-[6-Chloro-2-[(3*R*)-3-(methylamino)-1-pyrrolidinyl]-5-quinolinyl]-
cyclohexaneacetamide;
N-[6-Chloro-2-[(3*R*)-3-[(2-hydroxyethyl)amino]-1-pyrrolidinyl]-5-quinolinyl]-
cyclohexaneacetamide;
N-[6-Chloro-2-[(3*S*)-3-(methylamino)-1-pyrrolidinyl]-5-quinolinyl]-
10 cyclohexaneacetamide;
N-[6-Chloro-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-pyrrolidinyl]-5-quinolinyl]-
cyclohexaneacetamide;
N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-piperidinyl]-5-quinolinyl]-cyclohexaneacetamide;
N-[2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-methyl-5-quinolinyl]-cyclohexaneacetamide;
15 *N*-[6-Methyl-2-(1-piperazinyl)-5-quinolinyl]-cyclohexaneacetamide;
N-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-glycine;
N-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]- β -alanine; and
6-Chloro-*N*-(cyclohexylmethyl)-2-(1-piperazinyl)-5-quinolinecarboxamide,
dihydrochloride.

20 Suitable pharmaceutically acceptable salts of compounds of formula (IB) include base salts
such as an alkali metal salt for example sodium, an alkaline earth metal salt for example
calcium or magnesium, an organic amine salt for example triethylamine, morpholine,
N-methylpiperidine, *N*-ethylpiperidine, procaine, dibenzylamine, *N,N*-dibenzylethylamine
25 or amino acids for example lysine. In another aspect, where the compound is sufficiently
basic, suitable salts include acid addition salts such as methanesulphonate, fumarate,
hydrochloride, hydrobromide, citrate, maleate and salts formed with phosphoric and
sulphuric acid. There may be more than one cation or anion depending on the number of
charged functions and the valency of the cations or anions. A preferred pharmaceutically
30 acceptable salt is a hydrochloride salt.

Suitable prodrugs of compounds of formula (IB) are compounds which are hydrolysed *in vivo* to form compounds of formula (IB). Thus for example where compounds of formula (IB) include a carboxy group, these may be in the form of pharmaceutically acceptable esters or amides.

5

Suitable pharmaceutically acceptable esters of formula (IB) for carboxy groups include C₁₋₆alkyl esters, for example methyl or ethyl; C₁₋₆alkoxymethyl esters, for example methoxymethyl; C₁₋₆alkanoyloxymethyl esters, for example pivaloyloxymethyl; phthalidyl esters; C₃₋₈cycloalkoxycarbonyloxyC₁₋₆alkyl esters, for example

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1-cyclohexylcarbonyloxyethyl; 1,3-dioxolan-2-ylmethyl esters, for example 5-methyl-1,3-dioxolan-2-ylmethyl; C₁₋₆alkoxycarbonyloxyethyl esters, for example 1-methoxycarbonyloxyethyl; aminocarbonylmethyl esters and mono- or di-N-(C₁₋₆alkyl) versions thereof, for example N,N-dimethylaminocarbonylmethyl esters and N-ethylaminocarbonylmethyl esters; and may be formed at any carboxy group in

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the compounds of this invention. An *in vivo* cleavable ester of a compound of the invention containing a hydroxy group is, for example, a pharmaceutically-acceptable ester which is cleaved in the human or animal body to produce the parent hydroxy group. Suitable pharmaceutically acceptable esters for hydroxy include C₁₋₆alkanoyl esters, for example acetyl esters; and benzoyl esters wherein the phenyl group may be substituted with aminomethyl or N- substituted mono- or di- C₁₋₆alkyl aminomethyl, for example 4-aminomethylbenzoyl esters and 4-N,N-dimethylaminomethylbenzoyl esters.

20

Pharmaceutically acceptable amides are similarly *in-vivo* hydrolysable to yield the parent acid, and include C₁₋₆alkylamides such as acetamide.

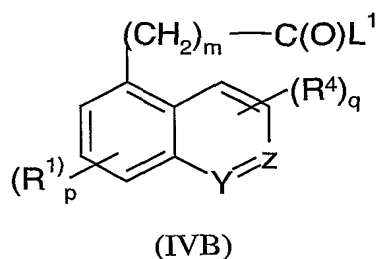
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The present invention further provides a process for the preparation of a compound of formula (IB) as defined above, or a pharmaceutically acceptable salt, prodrug or solvate thereof, which comprises either:

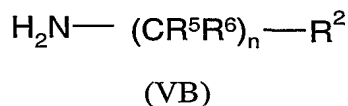
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(a) reacting a compound of formula (IVB)

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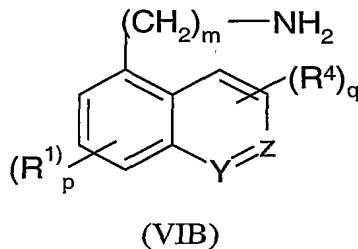
wherein L^1 represents a leaving group (e.g. hydroxyl or halogen) and Y, Z, R^1 , R^4 , m, p
 5 and q are as defined in formula (IB), with a compound of formula (VB),



R^2 , R^5 , R^6 and n are as defined in formula (IB); or

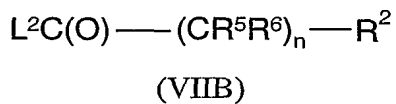
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(b) reacting a compound of formula (VIB)



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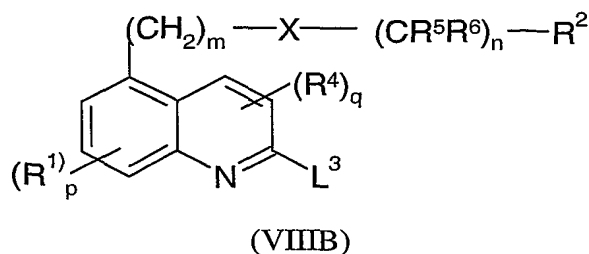
wherein Y, Z, R^1 , R^4 , m, p and q are as defined in formula (IB), with a compound of
 formula (VIIB)



20 wherein L^2 represents a leaving group (e.g. hydroxyl or halogen) and R^2 , R^5 , R^6 and n are
 as defined in formula (IB); or

(c) when Y is N and Z is CR^3 , and R^3 represents a group of formula (IIB) above where s is
 1 and X is $>NR^{11}$, reacting a compound of formula (VIIB)

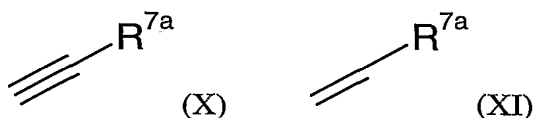
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wherein L^3 is a leaving group (e.g. halogen, paratoluene sulphonate or methane

5 sulphonate), and all other variables are as defined in relation to formula (IB), with a compound of formula (IXB), $H-N(R^{11})-R^9-R^{10}$, wherein R^9 , R^{10} and R^{11} are as defined in formula (IIB); or

(d) when Y is N and Z is CR^3 , and R^3 is a group R^7 where R^7 is optionally substituted C_3 -
 10 C_{10} alkyl group, reacting a compound of formula (VIIB) as defined in (c) above with a compound of formula (XB) or (XIB)



wherein R^{7a} represents a C_1 - C_7 alkyl group optionally substituted as defined for R^7 in
 15 formula (IB), optionally followed by a hydrogenation reaction; or

(e) when Y is N and Z is CR^3 , and R^3 is a group of formula (IIB) where s is 0, R^9 is $(CH_2)_2$ and R^{10} is $-NR^{19}R^{20}$, reacting a compound of formula (VIIB) as defined in (c) above with a compound of formula (XIIB)

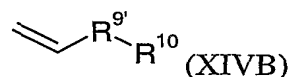


wherein L^4 is a leaving group (eg. trialkyltin, dialkylboron or zinc), followed by reaction with a compound of formula (XIIB), $HNR^{19}R^{20}$, wherein R^{19} and R^{20} are as defined above;

(f) when Y is N and Z is CR^3 , and R^3 is a group of formula (IIB) where s is 0, R^9 is $(CH_2)_2$ and R^{10} is $-NR^{19}R^{20}$, reacting a compound of formula (VIIB) as defined in (c) above with a compound of formula (XIIB) as defined in (e) above, followed by an oxidation reaction

and then by reaction with a compound of formula (XIIB) as defined in (e) above under reductive amination conditions; or

- (g) when Y is N and Z is CR³, and R³ is a group of formula (IIB) where s is 0, reacting a
5 compound of formula (VIII B) as defined in (c) above with a compound of formula (XIV B)



- wherein R⁹ is suitably defined such that saturation of the alkene and combination with R⁹
gives a group of formula R⁹ as defined in formula (IIB) and R¹⁰ is as defined in formula
10 (IIB), followed by removal of any protecting groups;

and optionally after (a), (b), (c), (d), (e), (f) or (g) carrying out one or more of the following:

- converting the compound obtained to a further compound of the invention
- 15 • forming a pharmaceutically acceptable salt, prodrug or solvate of the compound.

- In processes (a) and (b) the coupling reaction is conveniently carried out in an organic solvent such as dichloromethane, *N,N*-dimethylformamide or 1-methyl-2-pyrrolidinone. If L¹ or L² represent a hydroxyl group, it may be necessary or desirable to use a coupling
20 agent such as bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP).

- In process (c) the reaction may be performed in an organic solvent such as acetonitrile, *N,N*-dimethylformamide or 1-methyl-2-pyrrolidinone, and in the presence of a suitable base such as sodium hydride, triethylamine or potassium carbonate.

25

- In process (d), if the compound of formula (VIII B) is reacted with a compound of formula (XB), then the reaction is conveniently carried out in an organic solvent such as acetonitrile, e.g. at ambient temperature (20°C), in the presence of catalytic bistriphenylphosphine dichloride palladium(0), copper (I) iodide and a base (e.g.
30 triethylamine). The subsequent hydrogenation reaction may use hydrogen gas with a catalyst such as 5% rhodium on carbon in a solvent, for example, ethyl acetate or ethanol, and at a pressure of 3 bar.

Alternatively, if the compound of formula (VIII B) is reacted with a compound of formula (XIB), then it is preferred if the compound of formula (XIB) is pre-treated by reaction with a hydroborating reagent (e.g. 9-borabicyclo[3.3.1]nonane or catecholborane) in an organic solvent such as diethyl ether or tetrahydrofuran at a temperature in the range from, e.g. 0°C to 80°C, in particular from 60°C to 70°C, for about 2 to 3 hours. The pre-treated compound is then reacted with the compound of formula (VIII B) in the presence of a suitable base (e.g. sodium hydroxide or tri-potassium orthophosphate) and a palladium catalyst (e.g. dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) dichloromethane adduct), typically at a temperature in the range from 25°C to 90°C, particularly from 60°C to 70°C, for about 2 to 24 hours.

In process (e), the reaction with the vinyl compound of formula (XIIB) may conveniently be carried out in a solvent such as *N,N*-dimethylformamide and in the presence of catalytic dichlorobis(triphenylphosphine) palladium, at elevated temperature, e.g. at about 70°C. The subsequent addition reaction with the compound of formula (XIIB) may be performed under acidic or basic conditions, for example, in acetic acid in a solvent such as methanol or *isopropanol* at elevated temperature, e.g. at about 100°C.

In process (f), the reaction of the vinyl compound of formula (XVIII B) may be performed by procedures analogous to those outlined in the previous paragraph on process (e). The subsequent oxidation reaction may be carried out under standard conditions, for example, by using ozone followed by treatment with dimethylsulfide or triphenylphosphine in a suitable solvent such as dichloromethane, or, by using osmium tetroxide and sodium periodate in a suitable solvent such as 1,4-dioxane and water. The reductive amination step may be conveniently carried out in the presence of a reducing agent such as sodium cyanoborohydride, triacetoxyborohydride or sodium borohydride, in a polar solvent such as methanol, ethanol or dichloromethane either alone or in combination with acetic acid.

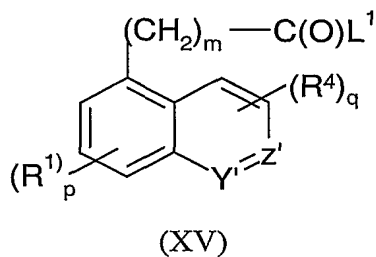
In process (g), the compound of formula (XIV B) is pre-treated by reaction with a hydroborating reagent (such as 9-borabicyclo[3.3.1]nonane or catecholborane) in a solvent.

(such as diethyl ether or tetrahydrofuran) at a temperature in the range from 0°C to 80°C (in particular from 60°C to 70°C) for about 2 to 3 hours, then cooling the reaction mixture to room temperature and adding a solution of a base (such as sodium hydroxide in water or *tri*-potassium orthophosphate in water) followed by a solution of the compound of formula (VIII) in a solvent (such as *N,N*-dimethylformamide) and a palladium catalyst (such as *tetrakis*(triphenylphosphine)palladium (II)). The resulting reaction mixture is stirred at a temperature in the range from 25°C to 90°C (particularly from 60°C to 70°C) for about 2 to 24 hours to yield the desired compounds of formula (IB).

Compounds of formulae (IVB), (VB), (VIB), (VIIB), (IXB), (XB), (XIB), (XIIB), (XIIIB) and (XIVB) are either commercially available, are known in the literature or may be prepared using known techniques.

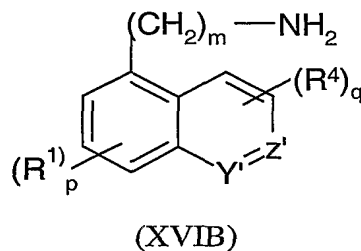
Compounds of formula (VIII B) are novel compounds and form a further aspect of the invention. Examples of preparation methods for certain of these compounds are given hereinafter in the examples. Other examples can be prepared by analogous methods. In particular, compounds of formula (VIII B) or analogues where Y is CL³ and Z is N can be prepared by either

(i) reacting a compound of formula (XVB)



wherein L¹ represents a leaving group (e.g. hydroxyl or halogen) and R¹, R⁴, m, p and q are as defined in formula (IB), and one of Y' or Z' is N and the other is a group CL³ where L³ is as defined in relation to formula (VIII B), with a compound of formula (VB) as defined above;

(ii) reacting a compound of formula (XVIB)



wherein R^1 , R^4 , m , p and q are as defined in formula (IB), Y' and Z' are as defined in relation to formula (XVB) with a compound of formula (VIIB) as defined above. Reaction conditions analogous to those described above in relation to steps (a) and (b) are suitably employed.

Compounds of formula (XVB) and (XVIB) are either commercially available, are known in the literature or may be prepared using known techniques.

Compounds of formula (IB) can be converted into further compounds of formula (IB) using standard procedures. For example, compounds of formula (IB) in which R^2 represents a halogen atom may be converted to a corresponding compound of formula (IB) in which

R^2 represents a C_1 - C_6 alkyl group by reaction with an alkyl Grignard reagent (e.g. methyl magnesium bromide) in the presence of a catalyst such as [1,3-

bis(diphenylphosphino)propane]dichloronickel (II) in a solvent such as tetrahydrofuran.

In a further example of the conversion of a compound of formula (IB) to another compound of formula (IB); a compound of formula (IB) where the group $NR^{13}R^{14}$ represents NH_2 may be converted into another compound of formula (IB) wherein R^{13} represents H and R^{14} is as defined in formula (IIIB), by treatment with an appropriate aldehyde (for example a suitably protected hydroxyl-acetaldehyde) in a reductive amination reaction. Suitable reducing agents include sodium cyanoborohydride, triacetoxyborohydride or sodium borohydride and the reaction may be carried out in a polar solvent such as methanol, ethanol or dichloromethane either alone or in combination with acetic acid.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (IB) above may involve, at various stages, the addition and removal of one or more protecting groups.

The protection and deprotection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

The compounds of formula (IB) above may be converted to a pharmaceutically acceptable salt or solvate thereof, preferably an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulphonate or *p*-toluenesulphonate, or an alkali metal salt such as a sodium or potassium salt. Other pharmaceutically acceptable salts, as well as prodrugs such as pharmaceutically acceptable esters and pharmaceutically acceptable amides may be prepared using conventional methods.

The compounds of the present invention are advantageous in that they possess pharmacological activity. They are therefore indicated as pharmaceuticals for use in the treatment of rheumatoid arthritis, osteoarthritis, psoriasis, allergic dermatitis, asthma, chronic obstructive pulmonary disease (COPD), hyperresponsiveness of the airway, septic shock, glomerulonephritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, atherosclerosis, growth and metastases of malignant cells, myoblastic leukaemia, diabetes, Alzheimer's disease, meningitis, osteoporosis, burn injury, ischaemic heart disease, stroke, varicose veins, sarcoidosis, rhinitis, acute and chronic pain, multiple sclerosis, myeloma, bone loss associated with malignancy and inflammatory and neurodegenerative diseases of the eye such as scleritis, episcleritis, uveitis, Sjogrens syndrome-keratoconjunctivitis, sclerokeratitis, optic neuritis, diabetic retinopathy, retinitis pigmentosa, antimalarial - induced retinopathy.

Accordingly, the present invention provides a compound of formula (IA) and/or (IB) or a pharmaceutically acceptable salt, prodrug or solvate thereof, as hereinbefore defined for use in therapy.

5

In another aspect, the invention provides the use of a compound of formula (IA) and/or (IB) or a pharmaceutically acceptable salt, prodrug or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

- 10 In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

- 15 The invention further provides a method of effecting immunosuppression (e.g. in the treatment of rheumatoid arthritis, osteoarthritis, irritable bowel disease, atherosclerosis or psoriasis) which comprises administering a therapeutically effective amount of a compound of formula (IA) and/or (IB) or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined to a patient.

- 20 The invention also provides a method of treating an obstructive airways disease (e.g. asthma or COPD) which comprises administering to a patient a therapeutically effective amount of a compound of formula (IA) and/or (IB) or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined to a patient.

- 25 For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated. The daily dosage of the compound of formula (IA) and/or (IB)/salt/solvate (active ingredient) may be in the range from 0.001 mg/kg to 30 mg/kg.

- 30 The compounds of formula (IA) and/or (IB) and pharmaceutically acceptable salts, prodrug and solvates thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (IA) and/or

(IB) compound/salt/solvate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.10 to 70 %w, of active ingredient, and, from 1 to 5 99.95 %w, more preferably from 30 to 99.90 %w, of a pharmaceutically acceptable adjuvant, diluent or carrier, all percentages by weight being based on total composition.

Thus, the present invention also provides a pharmaceutical composition comprising a compound of formula (IA) and/or (IB) or a pharmaceutically acceptable salt or solvate 10 thereof, as hereinbefore defined in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical composition of the invention may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane 15 aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally.

The invention further relates to combination therapies for the treatment of any one of 20 rheumatoid arthritis, osteoarthritis, osteoporosis, psoriasis, inflammatory bowel diseases, COPD, asthma, allergic rhinitis or cancer or the neurodegenerative diseases such as multiple sclerosis, Alzheimer's disease or stroke.

For the treatment of rheumatoid arthritis, the compounds of the invention may be 25 combined with "biological agents" such as TNF- α inhibitors such as anti-TNF monoclonal antibodies (such as Remicade, CDP-870 and Humira) and TNF receptor immunoglobulin molecules (such as Enbrel.reg.). IL-1 receptor antagonist (such as Anakinra) and IL-1 trap, IL-18 receptor, anti-IL-6 Ab, anti-CD20 Ab, anti-IL-15 Ab and CTLA4Ig.

30 Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as

naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin. The COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib and etoricoxib) and the cyclo-oxygenase inhibiting nitric oxide donors (CINOD's) and the "disease modifying agents" (DMARDs) such as methotrexate, sulphasalazine, cyclosporine A, lefunomide; ciclesonide; hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold.

The present invention still further relates to the combination of a compound of the invention together with a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist selected from the group consisting of zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; N-(5-substituted)-thiophene-2-alkylsulfonamides; 2,6-di-tert-butylphenol hydrazones; methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; pyridinyl-substituted 2n cyanonaphthalene compounds such as L-739,010; 2-cyanoquinoline compounds such as L-746,530; indole and quinoline compounds such as MK-591, MK-886, and BAY x 1005.

The present invention still further relates to the combination of a compound of the invention together with a receptor antagonists for leukotrienes LTB₄, LTC₄, LTD₄, and LTE₄ selected from the group consisting of the phenothiazin-3-ones such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

The present invention still further relates to the combination of a compound of the invention together with a PDE4 inhibitor including inhibitors of the isoform PDE4D.

The present invention still further relates to the combination of a compound of the

invention together with a antihistaminic H₁ receptor antagonists including cetirizine, loratadine, desloratadine, fexofenadine, astemizole, azelastine, and chlorpheniramine.

5 The present invention still further relates to the combination of a compound of the invention together with a gastroprotective H₂ receptor antagonist or the proton pump inhibitors (such as omeprazole)

The present invention still further relates to the combination of a compound of the invention together with an α_1 - and α_2 -adrenoceptor agonist vasoconstrictor
10 sympathomimetic agent, including propylhexedrine, phenylephrine, phenylpropanolamine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, and ethylnorepinephrine hydrochloride.

15 The present invention still further relates to the combination of a compound of the invention together with anticholinergic agents including ipratropium bromide; tiotropium bromide; oxitropium bromide; pirenzepine; and telenzepine.

The present invention still further relates to the combination of a compound of the invention together with a β_1 - to β_4 -adrenoceptor agonists including metaproterenol
20 isoproterenol, isoprenaline, albuterol, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, and pirbuterol; or methylxanthanines including theophylline and aminophylline; sodium cromoglycate; or muscarinic receptor (M1, M2, and M3) antagonist.

25

The present invention still further relates to the combination of a compound of the invention together with other modulators of chemokine receptor function such as CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR3, CXCR4 and CXCR5 (for the C-X-C
30 family) and CX₃CR1 for the C-X₃-C family.

The present invention still further relates to the combination of a compound of the invention together with an insulin-like growth factor type I (IGF-1) mimetic.

- 5 The present invention still further relates to the combination of compound of the invention together with an inhaled glucocorticoid with reduced systemic side effects, including prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, and mometasone furoate.
- 10 The present invention still further relates to the combination of a compound of the invention together with (a) tryptase inhibitors; (b) platelet activating factor (PAF) antagonists; (c) interleukin converting enzyme (ICE) inhibitors; (d) IMPDH inhibitors; (e) adhesion molecule inhibitors including VLA-4 antagonists; (f) cathepsins; (g) MAP kinase inhibitors; (h) glucose-6 phosphate dehydrogenase inhibitors; (i) kinin-B₁ - and B₂ -
- 15 receptor antagonists; (j) anti-gout agents, e.g., colchicine; (k) xanthine oxidase inhibitors, e.g., allopurinol; (l) uricosuric agents, e.g., probenecid, sulfinpyrazone, and benzbromarone; (m) growth hormone secretagogues; (n) transforming growth factor (TGF β); (o) platelet-derived growth factor (PDGF); (p) fibroblast growth factor, e.g., basic fibroblast growth factor (bFGF); (q) granulocyte macrophage colony stimulating factor
- 20 (GM-CSF); (r) capsaicin cream; (s) Tachykinin NK₁ and NK₃ receptor antagonists selected from the group consisting of NKP-608C; SB-233412 (talnetant); and D-4418; and (t) elastase inhibitors selected from the group consisting of UT-77 and ZD-0892 (u) induced nitric oxide synthase inhibitors (iNOS) or (v) chemoattractant receptor-homologous molecule expressed on TH2 cells, (CRTH2 antagonists).
- 25 The present invention still further relates to the combination of a compound of the invention together with an inhibitor of matrix metalloproteases (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1
- 30 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11).

The compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, induced nitric oxide synthase inhibitors (iNOS inhibitors), COX-2 inhibitors such as celecoxib, valdecoxib, rofecoxib and etoricoxib, and the cyclo-oxygenase inhibiting nitric oxide donors (CINOD's) analgesics (such as paracetamol and tramadol), cartilage sparing agents such as diacerein, doxycycline and glucosamine, and intra-articular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc.

The compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of inflammatory bowel diseases (Ulcerative colitis and Crohn's disease). Suitable agents to be used include sulphasalazine, 5-amino-salicylates, the thiopurines, azathioprine and 6-mercaptopurine and corticosteroids such as budesonide.

The compounds of the present invention may also be used in combination with anticancer agents such as endostatin and angiostatin or cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and farnesyl transferase inhibitors, VegF inhibitors, COX-2 inhibitors and antimetabolites such as methotrexate, antineoplastic agents, especially antimitotic drugs including the vinca alkaloids such as vinblastine and vincristine.

The compounds of the invention may also be used in combination with antiviral agents such as Viracept, AZT, aciclovir and famciclovir, and antiseptis compounds such as Valant.

The compounds of the present invention may also be used in combination with

cardiovascular agents such as calcium channel blockers, lipid lowering agents such as statins, fibrates, beta-blockers, Ace inhibitors, Angiotensin-2 receptor antagonists and platelet aggregation inhibitors.

- 5 The compounds of the present invention may also be used in combination with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, Requip, Mirapex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, Nicotine agonists, Dopamine agonists and inhibitors of neuronal nitric oxide synthase), and
10 anti Alzheimer's drugs such as donepezil, tacrine, COX-2 inhibitors, propentofylline or metryfonate.

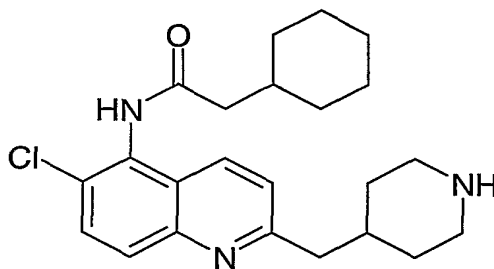
- The compounds of the present invention may also be used in combination with osteoporosis agents such as roloxifene, droloxifene, lasofoxifene or fosomax and
15 immunosuppressant agents such as FK-506, rapamycin, cyclosporine, azathioprine, and methotrexate.

- The present invention will now be further explained by reference to the following illustrative examples. In the examples the NMR spectra were measured on a Varian Unity
20 spectrometer at a proton frequency of either 300 or 400 MHz. The MS spectra were measured on either an Agilent 1100 MSD G1946D spectrometer or a Hewlett Packard HP1100 MSD G1946A spectrometer. Preparative HPLC separations were performed using a Waters Symmetry® or Xterra® column using 0.1% aqueous trifluoroacetic acid: acetonitrile, 0.1% aqueous ammonia: acetonitrile or 0.1% ammonium acetate: acetonitrile
25 as the eluent.

- The present invention will now be further explained by reference to the following illustrative examples. In the examples the NMR spectra were measured on a Varian Unity spectrometer at a proton frequency of either 300 or 400 MHz. The MS spectra were
30 measured on either an Agilent 1100 MSD G1946D spectrometer or a Hewlett Packard HP1100 MSD G1946A spectrometer. Preparative HPLC separations were performed using

a Waters Symmetry[®] or Xterra[®] column using 0.1% aqueous trifluoroacetic acid: acetonitrile, 0.1% aqueous ammonia: acetonitrile or 0.1% ammonium acetate: acetonitrile as the eluent. Microwave reactions were performed in a CEM Discover single mode microwave.

5

Example 1***N*-[6-Chloro-2-(4-piperidinylmethyl)-5-quinolinyl]-cyclohexaneacetamide, dihydrochloride**

10

a) *N*-(2,6-Dichloro-5-quinolinyl)-cyclohexaneacetamide

To a stirred solution of 2,6-dichloroquinolin-5-amine (prepared as described in (d) below) (1 g) in *N*-methyl pyrrolidinone (12 mL) was added 4-*N,N*-dimethylaminopyridine (1.2 g), cyclohexaneacetic acid (1 g) and PyBroP (4.4 g). The reaction mixture was heated to 50°C for 10 hours. The mixture was cooled to room temperature and poured into water (10 mL) which was subsequently acidified to pH1 with aqueous 2M hydrochloric acid. The resulting solution was extracted with dichloromethane (3x20 mL). The combined organic extracts were dried, filtered and partially concentrated to give a white precipitate which was removed by filtration. Purification by chromatography (SiO₂, methanol:dichloromethane 1:10 as eluant) gave the sub-title compound (490 mg).

15

20

¹H NMR (400 MHz, d₆-DMSO) δ 10.07 (1H, s), 8.25 (1H, d), 7.94 (2H, s), 7.70 (1H, d), 2.37 (2H, d), 1.83-1.63 (6H, m), 1.33-1.00 (5H, m).

MS: APCI(+ve) 337/339 (M+H⁺).

25

b) 4-[[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]methyl]-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester

9-Borabicyclo[3.3.1]nonane dimer solution (3.5 mL, 2M in tetrahydrofuran) was added to 4-methylene-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester (prepared according to the method of Journal of Medicinal Chemistry 2002, **45**, 3143) (345 mg) at room temperature under nitrogen. The mixture was refluxed for 3 hours after which it was cooled to room temperature. Potassium phosphate (1 g) in water (1 mL) was added and the mixture stirred for 30 minutes. *N*-(2,6-Dichloro-5-quinolinyl)-cyclohexaneacetamide (Example 1 (a)) (300 mg) in *N,N*-dimethylformamide (2 mL) was added followed by *tetrakis*(triphenylphosphine)palladium(0) (20 mg). The reaction mixture was heated to 80-90°C for 4 hours under nitrogen. On cooling to room temperature the reaction mixture was filtered through diatomaceous earth and the tetrahydrofuran removed under vacuum. The resulting mixture was poured into water and extracted with ethyl acetate. The combined organic extracts were dried, filtered and evaporated. Purification (SiO₂, ethyl acetate:isohexane 20:80 as eluant) gave the sub-titled compound (200 mg).

MS: APCI(+ve) 500/502 (M+H⁺).

c) *N*-[6-Chloro-2-(4-piperidinylmethyl)-5-quinolinyl]-cyclohexaneacetamide, dihydrochloride

4-[[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]methyl]-1-piperidinecarboxylic acid, 1,1-dimethylethyl ester (Example 1(b)) was dissolved in methanol (0.5 mL) and dichloromethane (3 mL). HCl in 1,4-dioxane (4M, 1 mL) was added and the mixture stirred for 1 hour. The resultant suspension was evaporated to dryness and recrystallised from methanol / ethyl acetate to give the title compound as a colourless solid (120 mg).

¹H NMR (400 MHz, CD₃OD) δ 8.89 (1H, d), 8.25 (2H, s), 8.08 (1H, d), 3.42 (2H, m), 3.01 (2H, dt), 2.52 (2H, d), 2.35 (1H, m), 2.00-1.84 (6H, m), 1.82-1.60 (6H, m), 1.43-1.09 (5H, m).

MS: APCI(+ve) 400/402 (M+H⁺).

m.p. 170-175 °C

d) 2,6-Dichloroquinolin-5-amine

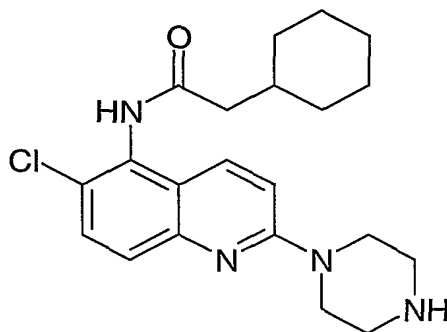
6-Chloro-5-nitroquinoline 1-oxide (4 g) was added to phosphorus oxychloride (15 mL) at 0°C. The solution was allowed to warm to room temperature and stirred for 12 hours. The excess phosphorus oxychloride was evaporated *in vacuo* and the residue dissolved in water (100 mL) / dichloromethane (100 mL). The layers were separated and the aqueous layer
5 extracted with dichloromethane (2x50 mL). The combined extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to give an oil. The residue was dissolved in ethanol/water (1:1, 80 mL), ammonium chloride (2.8 g) and iron (2.8 g) added. The mixture was stirred at 65°C for 4 hours, cooled to room temperature and filtered. The resulting solid was suspended in dimethylsulfoxide (50 mL), methanol (50
10 mL) and aqueous hydrochloric acid added (2M, 100 mL). The resulting solid was removed by filtration and then treated with ether (50 mL) and *isohexane* (50 mL). Evaporation of the mixture afforded the sub-title compound as a solid (1 g).

¹H NMR (400 MHz, DMSO-d₆) δ 8.73 (1H, dd,); 7.62 (1H, d); 7.51 (1H, d); 7.13 (1H, dd);
15 6.36 (2H, s).

MS: APCI(+ve) 213/215 (M+H⁺)

Example 2

N-[6-Chloro-2-(1-piperazinyl)-5-quinolinyl]-cyclohexaneacetamide, dihydrochloride



To a stirred solution of *N*-(2,6-dichloro-5-quinolinyl)-cyclohexaneacetamide (Example 1
(a)) (170 mg) and potassium carbonate (350 mg) in *N*-methyl pyrrolidinone (4 mL) was
added piperazine (600 mg). The mixture was heated at 120°C for 3 hours after which it was
cooled and poured into water. The mixture was extracted with dichloromethane and the
25 combined extracts evaporated to give a residue which was then partitioned between water
and ethyl acetate. The organic layer was separated and the aqueous layer further extracted

with ethyl acetate. The combined organic extracts were concentrated to give a residue which was purified by chromatography (SiO₂, methanol:dichloromethane:ammonium hydroxide solution 19:80:1 as eluant) and the resultant product was converted to its hydrochloride salt by treatment with hydrochloric acid (4M in 1,4-dioxane).

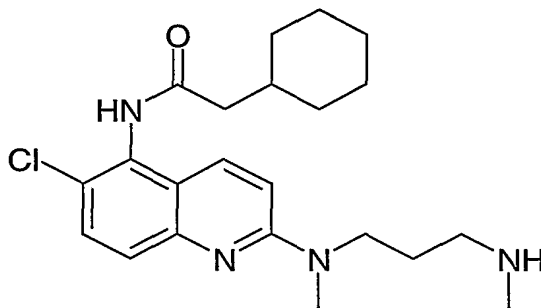
5 Recrystallisation (methanol / ethyl acetate) afforded the title compound as a solid (80 mg).

¹H NMR (400 MHz, d₆-DMSO) δ 9.92 (1H, s), 9.30 (2H, s), 7.97 (1H, d), 7.70-7.59 (2H, m), 7.41 (1H, d), 4.01-3.92 (4H, m), 3.27-3.17 (4H, m), 2.35 (2H, d), 1.89-1.60 (6H, m), 1.33-0.98 (5H, m).

10 MS: APCI(+ve) 387/389 (M+H⁺).
m.p. >250°C

Example 3

N-[6-Chloro-2-[methyl[3-(methylamino)propyl]amino]-5-quinolinyl]-
15 cyclohexaneacetamide, dihydrochloride



Prepared according to the method of example 2, using *N*-(2,6-dichloro-5-quinolinyl)-
20 cyclohexaneacetamide (Example 1 (a)) (100 mg) and *N,N'*-dimethyl-1,3-propanediamine (300 mg). Further purification by HPLC (Symmetry - 0.1% aqueous trifluoroacetic acid / acetonitrile) followed by conversion to its hydrochloride salt as described in example 2, afforded the title compound as a solid (56 mg).

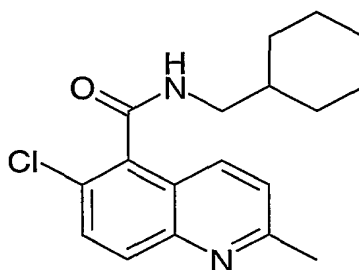
^1H NMR (400 MHz, CD_3OD) δ 7.95 (1H, d), 7.61 (2H, s), 7.17 (1H, d), 3.63 (1H, t), 3.16 (3H, s), 2.93 (2H, t), 2.81 (2H, t), 2.58 (3H, s), 2.34 (2H, d), 2.02 (2H, t), 1.80-1.77 (1H, m), 1.70 (2H, d), 1.62 (1H, d), 1.30-1.13 (4H, m), 1.04 (2H, q).

MS: APCI(+ve) 403/405 ($\text{M}+\text{H}^+$).

5 m.p. 231-233°C

Example 4

6-Chloro-*N*-(cyclohexylmethyl)-2-methyl-5-quinolinecarboxamide, hydrochloride



10

a) 6-Chloro-*N*-(cyclohexylmethyl)-2-methyl-5-quinolinecarboxamide, hydrochloride

To a stirred solution of 6-chloro-2-methyl-5-quinolinecarboxylic acid (prepared as described in example 4 (b)) (250 mg) in dichloromethane (5 mL) at 0°C under nitrogen, was added *N,N*-dimethylformamide (1 drop) and oxalyl chloride (0.4 mL). The reaction mixture was stirred at room temperature for 1 hour, then evaporated to dryness and redissolved in dichloromethane (3 mL). This solution was cooled to 0°C and a mixture of cyclohexanemethylamine (128 mg) and triethylamine (1 mL) in dichloromethane (2 mL) was added dropwise. The reaction mixture was stirred at room temperature for 1 hour then poured into saturated aqueous sodium hydrogen carbonate (20 mL). The mixture was extracted with dichloromethane (3×20 mL) and the combined extracts were dried, filtered and evaporated. Purification (SiO_2 , ethyl acetate:*isohexane* 3:2 as eluant) gave the title compound as a solid (35 mg).

^1H NMR (400 MHz, d_6 -DMSO) δ 8.85 (1H, t), 8.33 (1H, d), 8.23 (1H, d), 7.99 (1H, d), 7.80 (1H, d), 3.22 (2H, t), 2.84 (3H, s), 1.85-1.52 (6H, m), 1.30-1.10 (3H, m), 1.06-0.93 (2H, m).

MS: APCI(+ve) 317/319 ($\text{M}+\text{H}^+$).

m.p. 210-213°C

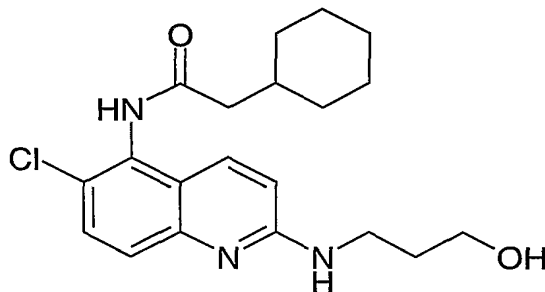
(b) 6-Chloro-2-methyl-5-quinolinecarboxylic acid

Crotonaldehyde (1.5 mL) was added dropwise over a period of 1 hour to a mixture of 5-amino-2-chlorobenzoic acid (1.7 g), ferrous sulphate heptahydrate (0.77 g), sodium *m*-nitrobenzenesulphonate (1.2 g) and concentrated hydrochloric acid (11 mL) at 95°C. The reaction mixture was heated for a further 15 minutes then filtered whilst still hot. The collected solid was extracted with boiling 2M aqueous hydrochloric acid solution (20 mL) and the extract combined with the filtrate. Ammonium acetate was then added to give a solution of pH 4, which was cooled in ice and the resultant precipitate collected by filtration and washed with water. The product was converted to its hydrochloride salt by treatment with hydrochloric acid (4M in 1,4-dioxane) and the solid dried *in vacuo* to give the sub-title compound (0.5 g) as a solid.

MS: APCI(+ve) 222/224 (M+1)

Example 5

***N*-[6-Chloro-2-[(3-hydroxypropyl)amino]-5-quinolinyl]-cyclohexaneacetamide, hydrochloride**



20

Prepared according to the method of example 2, using *N*-(2,6-dichloro-5-quinolinyl)-cyclohexaneacetamide (Example 1 (a)) (200 mg) and 3-amino-1-propanol (540 mg). Water was added to the residue and the product was collected by filtration. The product was converted to its hydrochloride salt by treatment with hydrochloric acid (4M in 1,4-dioxane). Recrystallisation (methanol / ethyl acetate) afforded the title compound as a solid (98 mg).

25

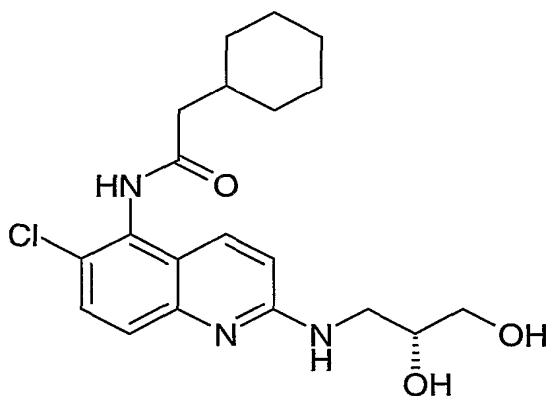
^1H NMR (400 MHz, d_6 -DMSO) δ 10.10 (1H, s), 8.11-7.97 (2H, m), 7.86 (1H, d), 7.22 (1H, d), 3.64 (2H, d), 3.56 (2H, t), 2.35 (2H, d), 1.91-1.57 (8H, m), 1.34-1.13 (3H, m), 1.04 (2H, q).

MS: APCI(+ve) 376/378 ($\text{M}+\text{H}^+$).

5 m.p. 240-244°C

Example 6

***N*-[6-Chloro-2-[[*(2R)*-2,3-dihydroxypropyl]amino]-5-quinolinyl]-cyclohexaneacetamide**



10

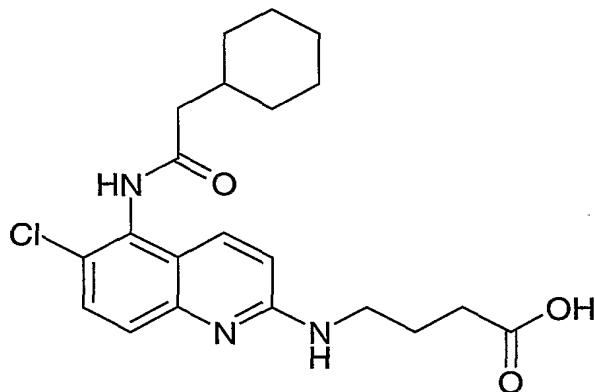
Prepared according to the method of example 2, using *N*-(2,6-dichloro-5-quinolinyl)-cyclohexaneacetamide (Example 1 (a)) (200 mg) and 3-amino-(*2R*)-1,2-propanediol (655 mg). Purification (SiO_2 , dichloromethane:methanol 9:1 as eluant) gave the title compound (20 mg).

15

^1H NMR (400 MHz, d_6 -DMSO) δ 9.74 (1H, s), 7.72 (1H, d), 7.54 (1H, d), 7.40 (1H, d), 6.91 (1H, d), 3.71-3.64 (1H, m), 3.59-3.50 (1H, m), 3.43-3.27 (3H, m), 2.31 (2H, d), 1.89-1.76 (3H, m), 1.75-1.58 (3H, m), 1.32-1.11 (3H, m), 1.10-0.97 (2H, m).

MS: APCI(+ve) 392/394 ($\text{M}+\text{H}^+$).

20 m.p. 155-159 °C

Example 7**4-[[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]amino]-butanoic acid****a) 4-[[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]amino]-butanoic acid, 1,1-dimethylethyl ester**

To a stirred solution of *N*-(2,6-dichloro-5-quinolinyl)-cyclohexaneacetamide (Example 1 (a)) (200 mg), potassium carbonate (410 mg) and *tetrabutylammonium* bromide (2 mg) in *N*-methyl pyrrolidinone (5 mL) was added 4-amino-butanoic acid 1,1-dimethylethyl ester (1 g). The mixture was heated at 130°C for 72 hours after which it was cooled and poured into water. The mixture was extracted with dichloromethane (3×20 mL) and the combined extracts dried, filtered and evaporated. Purification (SiO₂, ethyl acetate:*isohexane* 3:7 as eluant) gave the sub-title compound (200 mg).

¹H NMR (400 MHz, d₆-DMSO) δ 9.71 (1H, s), 7.71 (1H, d), 7.52 (1H, d), 7.41 (1H, d), 6.80 (1H, d), 3.48-3.24 (2H, m), 2.38-2.23 (4H, m), 1.96-1.55 (8H, m), 1.40 (9H, s), 1.33-0.97 (5H, m).

b) 4-[[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]amino]-butanoic acid

4-[[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]amino]-butanoic acid 1,1-dimethylethyl ester (Example 7 (a)) (200 mg) was dissolved in dichloromethane (3 mL). Trifluoroacetic acid (1 mL) was added and the mixture stirred for 3 hours. The resultant suspension was evaporated to dryness and recrystallised from acetonitrile to give the title compound (20 mg).

^1H NMR (400 MHz, d_6 -DMSO) δ 12.06 (1H, s), 9.72 (1H, s), 7.71 (1H, d), 7.51 (1H, d), 7.42 (1H, d), 7.21 (1H, t), 6.80 (1H, d), 3.48-3.23 (2H, m), 2.37-2.27 (4H, m), 1.87-1.58 (8H, m), 1.33-1.12 (3H, m), 1.09-0.97 (2H, m).

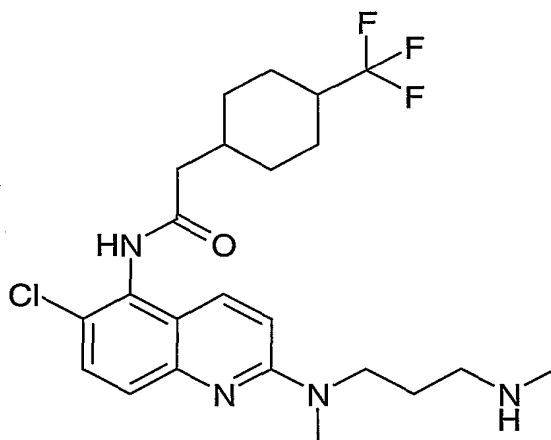
MS: APCI(+ve) 404/406 ($\text{M}+\text{H}^+$).

5 m.p. 248-250 °C

Example 8

N-[6-Chloro-2-[methyl[3-(methylamino)propyl]amino]-5-quinolinyl]-4-(trifluoromethyl)-cyclohexaneacetamide, dihydrochloride

10



a) [4-(Trifluoromethyl)cyclohexylidene]-acetic acid, ethyl ester

A suspension of sodium hydride (60 % in oil, 277 mg) in hexane was stirred under nitrogen for 10 minutes and the solvent was decanted. The residue was then suspended in tetrahydrofuran (10 mL) and cooled to 0°C. Triethyl phosphonoacetate (1.5 mL) in tetrahydrofuran (10 mL) was added dropwise and the reaction mixture stirred at room temperature for 30 minutes. The mixture was then cooled to 0°C and 4-(trifluoromethyl)-cyclohexanone (1 g) in tetrahydrofuran (2 mL) was added dropwise. The reaction was stirred at room temperature for 16 hours. The mixture was then quenched by careful addition of saturated aq. NH_4Cl solution. The resulting solution was extracted with ether (3x15 mL). The combined organic extracts were washed with brine (2x10 mL), dried, filtered and evaporated. Purification (SiO_2 , ethyl acetate:isohexane 2:98 as eluant) gave the sub-title compound as a colourless oil (1 g).

¹H NMR (400 MHz, d₆-DMSO) δ 5.70 (1H, s), 4.07 (2H, q), 3.84-3.73 (1H, m), 2.70-2.48 (1H, m), 2.38 (1H, d), 2.26 (1H, td), 2.08-1.92 (3H, m), 1.42-1.22 (2H, m), 1.19 (3H, t).

b) 4-(Trifluoromethyl)-cyclohexaneacetic acid

- 5 To a stirred solution of [4-(trifluoromethyl)cyclohexylidene]-acetic acid, ethyl ester (Example 8 (a)) (1 g) in ethyl acetate (20 mL) was added 5 % palladium on carbon (450 mg). The mixture was stirred at room temperature under a 2 bar atmosphere of hydrogen. The reaction mixture was then filtered through diatomaceous earth and concentrated. Purification (SiO₂, ethyl acetate:isohexane 1:19 as eluant) gave 4-(trifluoromethyl)-
10 cyclohexaneacetic acid, ethyl ester (800 mg), which was dissolved in methanol (3 mL). Potassium hydroxide (1 g) in water (3 mL) was added and the mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated and subsequently acidified to pH1 with aqueous 2M hydrochloric acid. The resulting solution was extracted with dichloromethane (3x10 mL) and the combined organic extracts dried, filtered and
15 evaporated to give the sub-title compound as an oil (660 mg).

GCMS: 210 (M⁺)

c) N-(2,6-Dichloro-5-quinolinyl)-4-(trifluoromethyl)-cyclohexaneacetamide

- 20 Prepared according to the method of example 1(a), using 2,6-dichloroquinolin-5-amine (prepared as described in Example 1(d) above) (400 mg) and 4-(trifluoromethyl)-cyclohexaneacetic acid (Example 8 (b)) (436 mg). Purification (SiO₂, dichloromethane:methanol 99:1 as eluant) gave the sub-title compound (350 mg).

- 25 ¹H NMR (400 MHz, d₆-DMSO) δ 10.11 (1H, s), 8.27 (1H, d), 7.94 (2H, s), 7.70 (1H, d), 3.36-3.28 (1H, m), 2.40 (2H, d), 1.98-1.56 (5H, m), 1.38-1.06 (4H, m).

d) N-[6-Chloro-2-[methyl[3-(methylamino)propyl]amino]-5-quinolinyl]-4-(trifluoromethyl)-cyclohexaneacetamide, dihydrochloride

- 30 Prepared according to the method of example 2 using N-(2,6-dichloro-5-quinolinyl)-4-(trifluoromethyl)-cyclohexaneacetamide (Example 8 (c)) (150 mg) and N,N'-dimethyl-1,3-propanediamine (450 mg). The product was converted to its hydrochloride salt by

treatment with hydrochloric acid (4M in 1,4-dioxane). Recrystallisation (methanol / ethyl acetate) afforded the title compound as a solid (40 mg).

^1H NMR (400 MHz, d_6 -DMSO) δ 8.12 (1H, d), 7.88 (1H, s), 7.79 (1H, d), 7.42 (1H, s),

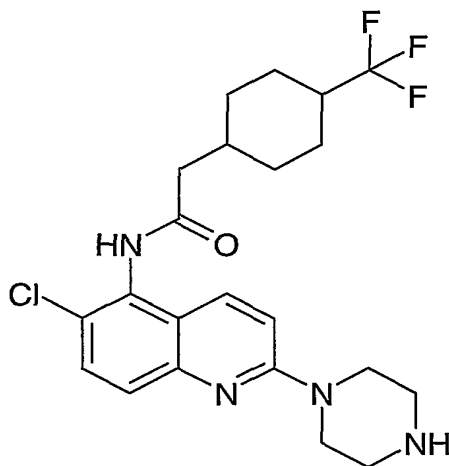
5 3.85 (2H, t), 3.35 (3H, s), 3.04 (2H, t), 2.64 (3H, s), 2.40 (2H, d), 2.10-1.98 (2H, m), 1.98-1.86 (3H, m), 1.86-1.75 (1H, m), 1.70-1.61 (1H, m), 1.36-1.04 (5H, m).

MS: APCI(+ve) 471/473 ($\text{M}+\text{H}^+$).

m.p. 250 °C dec.

10 Example 9

***N*-[6-Chloro-2-(1-piperazinyl)-5-quinolinyl]-4-(trifluoromethyl)-cyclohexaneacetamide**



15 Prepared according to the method of example 2 using *N*-(2,6-dichloro-5-quinolinyl)-4-(trifluoromethyl)-cyclohexaneacetamide (Example 8 (c)) (200 mg) and piperazine (420 mg). Purification (SiO_2 , dichloromethane:methanol 95:5 as eluant) afforded the title compound as a solid (55 mg).

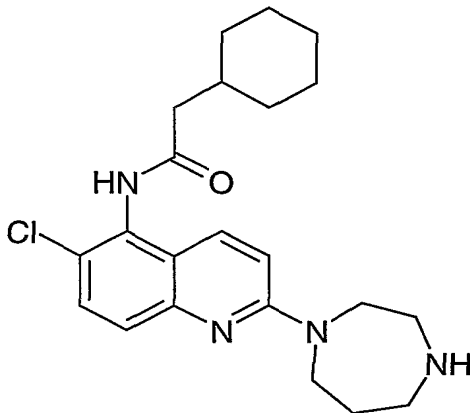
20 ^1H NMR (400 MHz, d_6 -DMSO) δ 9.82 (1H, s), 7.85 (1H, d), 7.57 (1H, d), 7.48 (1H, d), 7.28 (1H, d), 3.66-3.56 (4H, m), 2.85-2.73 (4H, m), 2.35 (2H, d), 2.30-2.15 (1H, m), 1.98-1.55 (5H, m), 1.36-1.04 (4H, m).

MS: APCI(+ve) 455/457 ($\text{M}+\text{H}^+$).

m.p. 186-190°C

Example 10

***N*-[6-Chloro-2-(hexahydro-1*H*-1,4-diazepin-1-yl)-5-quinolinyl]-cyclohexaneacetamide**



Prepared according to the method of example 2 using *N*-(2,6-dichloro-5-quinolinyl)-cyclohexaneacetamide (Example 1 (a)) (200 mg) and homopiperazine (600 mg).
Recrystallisation from acetonitrile afforded the title compound as a solid (96 mg).

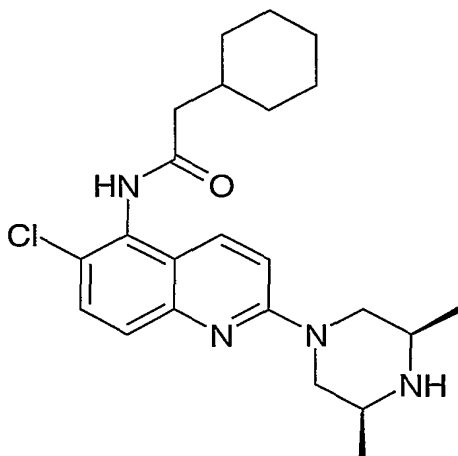
¹H NMR (400 MHz, d₆-DMSO) δ 9.75 (1H, s), 7.81 (1H, d), 7.53 (1H, d), 7.44 (1H, d), 7.14 (1H, d), 3.94-3.65 (4H, m), 2.87 (2H, t), 2.65 (2H, t), 2.32 (2H, d), 1.92-1.59 (8H, m), 1.34-0.97 (5H, m).

MS: APCI(+ve) 401/403 (M+H⁺).

m.p. 186-188°C

Example 11

***N*-[6-Chloro-2-[(*cis*-3,5-dimethyl-1-piperazinyl)-5-quinolinyl]-cyclohexaneacetamide**



Prepared according to the method of example 2 using *N*-(2,6-dichloro-5-quinolinyl)-cyclohexaneacetamide (Example 1 (a)) (150 mg) and *cis*-2,6-dimethylpiperazine (500 mg). Purification (SiO₂, dichloromethane:methanol 95:5 as eluant) and recrystallisation from methanol afforded the title compound as a solid (32 mg).

5

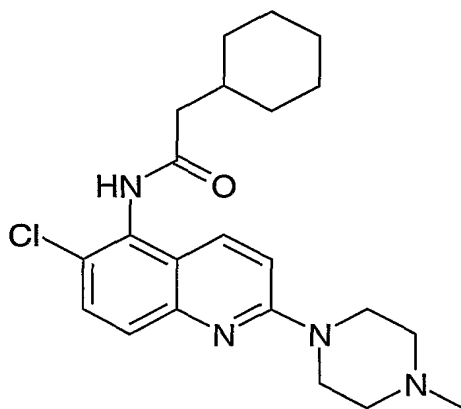
¹H NMR (400 MHz, d₆-DMSO) δ 9.77 (1H, s), 7.83 (1H, d), 7.56 (1H, d), 7.48 (1H, d), 7.31 (1H, d), 4.40 (2H, d), 2.80-2.69 (2H, m), 2.42-2.27 (4H, m), 1.90-1.58 (6H, m), 1.34-0.95 (11H, m).

MS: APCI(+ve) 415/417 (M+H⁺).

10 m.p. 250-252°C

Example 12

***N*-[6-Chloro-2-(4-methyl-1-piperazinyl)-5-quinolinyl]-cyclohexaneacetamide, dihydrochloride**



15

Prepared according to the method of example 2 using *N*-(2,6-dichloro-5-quinolinyl)-cyclohexaneacetamide (Example 1 (a)) (150 mg) and 1-methyl-piperazine (380 mg). The product was purified by chromatography (SiO₂, dichloromethane:methanol 95:5 as eluant), converted to its hydrochloride salt by treatment with hydrochloric acid (4M in 1,4-dioxane) and recrystallised (methanol / ethyl acetate) to give the title compound as a solid (40 mg).

20

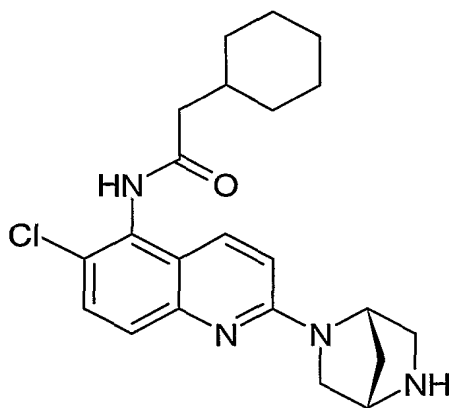
¹H NMR (400 MHz, d₆-DMSO) δ 11.14 (1H, s), 9.97 (1H, s), 8.02 (1H, d), 7.83-7.65 (2H, m), 7.47 (1H, d), 4.71 (2H, d), 3.51 (4H, t), 3.20-3.05 (2H, m), 2.79 (3H, d), 2.35 (2H, d), 1.90-1.59 (6H, m), 1.34-0.99 (5H, m).

MS: APCI(+ve) 401/403 (M+H⁺).

5 m.p. 270°C dec.

Example 13

***N*-[6-Chloro-2-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-5-quinolinyl]-cyclohexaneacetamide, acetate**



10

Prepared according to the method of example 2 using *N*-(2,6-dichloro-5-quinolinyl)-cyclohexaneacetamide (Example 1 (a)) (200 mg) and (1*S*,4*S*)-2,5-

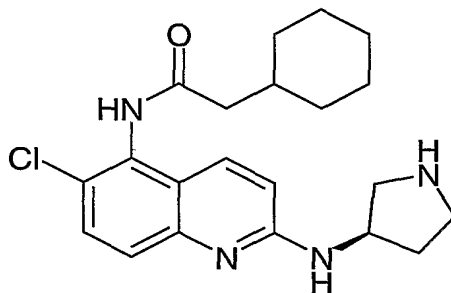
15 dichloromethane:methanol 90:10 as eluant) and further purification by HPLC (Symmetry - 0.1% aqueous ammonium acetate / acetonitrile) afforded the title product (12 mg).

¹H NMR (400 MHz, d₆-DMSO) δ 9.43 (1H, s), 7.82 (1H, d), 7.50 (1H, d), 7.43 (1H, d), 6.89 (1H, d), 4.85 (1H, s), 3.70 (1H, s), 3.54 (1H, dd), 3.35 (1H, d), 2.97 (1H, d), 2.83 (1H, d), 2.36-2.27 (2H, m), 1.92-1.59 (8H, m), 1.34-0.99 (5H, m).

20

MS: APCI(+ve) 399/401 (M+H⁺).

m.p. 120 °C dec.

Example 14***N*-[6-Chloro-2-[(3*R*)-3-pyrrolidinylamino]-5-quinoliny]-cyclohexaneacetamide, dihydrochloride**

To a stirred solution of *N*-(2,6-dichloro-5-quinoliny)-cyclohexaneacetamide (Example 1 (a)) (200 mg) and *tetra*-butylammonium bromide (750 mg) in *N*-methyl pyrrolidinone (2 mL) was added 1-(phenylmethyl)-(3*R*)-3-pyrrolidinamine (1 g). The mixture was heated at 130 °C for 72 hours before being cooled to room temperature and partitioned between water and ethyl acetate. The aqueous layer was further extracted with ethyl acetate. The combined organic extracts were concentrated and the residue was purified (SiO₂, methanol:dichloromethane 7:93 as eluant) to give a brown oil containing *N*-[6-chloro-2-[[3*R*)-1-(phenylmethyl)-3-pyrrolidinyl]amino]-5-quinoliny]-cyclohexaneacetamide. The oil was dissolved in dichloroethane (2 mL). 1-Chloroethyl chloroformate (0.03 mL) was added and the reaction heated to reflux for 6 hours. The mixture was then allowed to cool and evaporated to dryness. The residue was dissolved in methanol and heated to reflux for 2 hours. The solution was cooled, filtered through sodium hydrogen carbonate and concentrated. Purification by chromatography (SiO₂, dichloromethane:methanol: ammonium hydroxide solution 80:20:1 as eluant) and then by HPLC (Symmetry - 0.1% aqueous ammonium acetate / acetonitrile) afforded the product which was converted to its hydrochloride salt by treatment with hydrochloric acid (4M in 1,4-dioxane) and recrystallised (methanol / ethyl acetate) to give the title product (18 mg).

¹H NMR (400 MHz, d₆-DMSO) δ 9.62 (1H, s), 9.36 (1H, s), 7.92 (1H, d), 7.87-7.76 (1H, m), 7.66 (1H, d), 7.03 (1H, d), 4.86 (1H, s), 3.66-3.17 (6H, m), 2.40-2.27 (2H, m), 2.12-2.00 (1H, m), 1.93-1.57 (5H, m), 1.43-0.98 (5H, m).

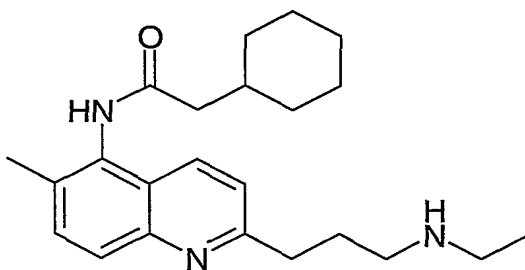
MS: APCI(+ve) 387/389 ($M+H^+$).

m.p. 193-198 °C

Example 15

5

***N*-[2-[3-(Ethylamino)propyl]-6-methyl-5-quinolinyl]-cyclohexaneacetamide, dihydrochloride**



10

a) *N*-(2-Chloro-6-methyl-5-quinolinyl)-cyclohexaneacetamide

To a solution of cyclohexaneacetyl chloride (prepared according to the method of J. Am. Chem. Soc. 1986, **108**, 7686) (560 mg) in dichloromethane (5 mL) was added a mixture of
15 2-chloro-6-methyl-5-quinolinamine (prepared according to the method of Journal of the American Chemical Society 1947, **69**, 179) (350 mg) and triethylamine (1 mL) in dichloromethane (5 mL) at 0°C. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was poured into saturated sodium bicarbonate solution and extracted with dichloromethane (3x20 mL). The combined organic extracts were dried,
20 filtered and evaporated to afford the sub-title compound (400 mg).

MS: APCI(+ve) 317/319 ($M+H^+$).

b) Ethyl-(2-propenyl)-carbamic acid, 1,1-dimethylethyl ester

25 Sodium hydride (60%, 0.25g) was added to *tert*-butyl allylcarbamate (1.0g) in anhydrous *N*-methylpyrrolidinone (4 ml) followed by ethyl iodide (1.6 ml). The crude product was

purified by chromatography (SiO₂, *isohexane*:ethyl acetate 19:1 as eluant) to afford the sub-title compound (0.53 g) as a colourless oil.

5 ¹H NMR (400MHz, CDCl₃) δ 5.78 (1H, m); 5.12 (2H, m); 3.80 (2H, s); 3.22 (2H, d); 1.46 (9H, s); 1.08 (3H, t).

c) [3-[5-[(Cyclohexylacetyl)amino]-6-methyl-2-quinoliny]propyl]ethyl-carbamic acid, 1,1-dimethylethyl ester

10 Prepared according to the method of example 1(b), using *N*-(2-chloro-6-methyl-5-quinoliny)-cyclohexaneacetamide (Example 15 (a)) (400 mg) and ethyl(2-propenyl)-carbamic acid, 1,1-dimethylethyl ester (Example 15 (b)) (277 mg). Purification (SiO₂, ethyl acetate:*isohexane* 20:80 as eluant) gave the sub-title compound (260 mg).

MS: APCI(+ve) 468 (M+H⁺).

15

d) *N*-[2-[3-(Ethylamino)propyl]-6-methyl-5-quinoliny]-cyclohexaneacetamide, dihydrochloride

20 Prepared according to the method of example 1(c), using [3-[5-[(cyclohexylacetyl)amino]-6-methyl-2-quinoliny]propyl]ethyl-carbamic acid, 1,1-dimethylethyl ester (Example 15 (c)) (250 mg) to afford the title compound (260 mg).

¹H NMR (400 MHz, d₆-DMSO) δ 9.70 (1H, s), 8.86 (2H, s), 8.38 (1H, d), 8.00 (1H, d), 7.75 (1H, d), 7.63 (1H, d), 3.18 (2H, t), 3.05-2.90 (4H, m), 2.47-2.39 (2H, m), 2.36 (3H, s), 2.21 (2H, quint.), 1.93-1.59 (6H, m), 1.39-1.06 (8H, m).

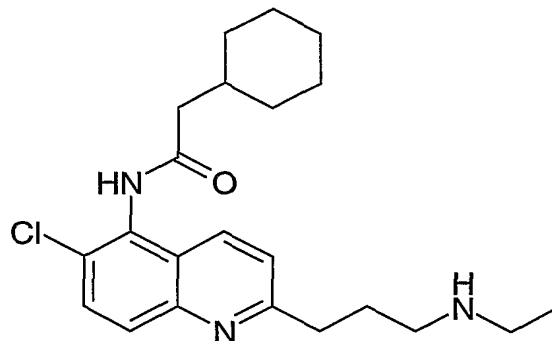
25 MS: APCI(+ve) 368 (M+H⁺).

m.p. 231-234°C

Example 16

30 ***N*-[6-Chloro-2-[3-(ethylamino)propyl]-5-quinoliny]-cyclohexaneacetamide, dihydrochloride**

85



Prepared according to the method of example 15, using *N*-(2,6-dichloro-5-quinolinyl)-cyclohexanecarboxamide (Example 1(a)) (500 mg) and ethyl(2-propenyl)-carbamate 1,1-dimethylethyl ester (330 mg). Recrystallisation (methanol / ethyl acetate) afforded the title compound as a solid (195 mg).

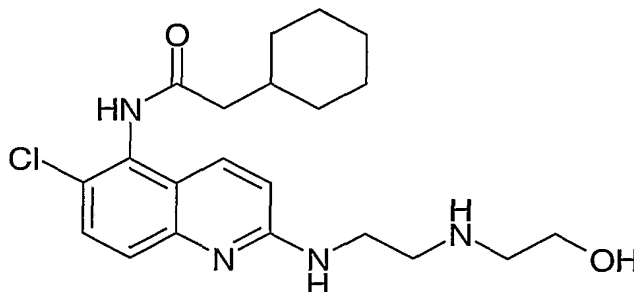
¹H NMR (400 MHz, d₆-DMSO) δ 10.18 (1H, s), 8.92 (2H, s), 8.37 (1H, d), 8.08 (1H, d), 7.96 (1H, d), 7.73 (1H, d), 3.21-3.09 (2H, m), 3.03-2.85 (4H, m), 2.39 (2H, d), 2.17 (2H, quint.), 1.94-1.55 (6H, m), 1.35-0.99 (8H, m).

MS: APCI(+ve) 388/390 (M+H⁺).

m.p. 152-155°C

Example 17

***N*-[6-Chloro-2-[[2-[(2-hydroxyethyl)amino]ethyl]amino]-5-quinolinyl]-cyclohexanecarboxamide, dihydrochloride**



To a stirred solution of *N*-(2,6-dichloro-5-quinolinyl)-cyclohexanecarboxamide (Example 1(a)) (170 mg) and potassium carbonate (350 mg) in *N*-methyl pyrrolidinone (4 mL) was added 2-[(2-aminoethyl)amino]-ethanol (500 μL). The mixture was heated at 120°C for 5

hours after which it was cooled and poured into water. The resulting solid was isolated by filtration, dried and suspended in dichloromethane (5 mL). The suspension was then treated with di-*tert*-butyl dicarbonate (220 mg) and triethylamine (200 μ L) and stirred for 2 hours. The mixture was poured into water and extracted with dichloromethane (3x20 mL).

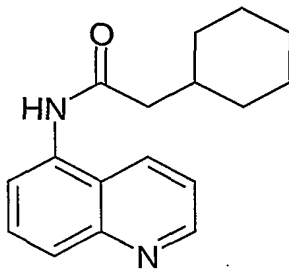
- 5 The combined organic layers were dried, filtered and concentrated. Purification (SiO_2 , methanol:dichloromethane solution 2.5:97.5 as eluant) yielded the desired isomer which was then dissolved in dichloromethane (5 mL) and methanol (0.5 mL), and treated with hydrochloric acid in 1,4-dioxane (4M, 1 mL) for 1 hour. The resultant suspension was evaporated to dryness and recrystallised from methanol / ethyl acetate to give the title
10 compound as a colourless solid (65 mg).

^1H NMR (400 MHz, d_6 -DMSO/ D_2O) δ 8.04 (1H, d), 7.94 (1H, d), 7.86 (1H, d), 7.16 (1H, d), 3.91 (2H, t), 3.75-3.65 (2H, m), 3.32 (2H, t), 3.11 (2H, t), 2.37 (2H, d), 1.90-1.60 (6H, m), 1.35-0.95 (5H, m).

- 15 MS: APCI(+ve) 405/407 ($\text{M}+\text{H}^+$).
m.p. 238-240°C

Example 18

N-5-Quinolinyl-cyclohexaneacetamide



20

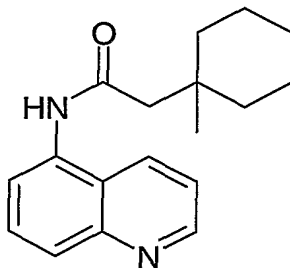
To a stirred solution of cyclohexaneacetic acid (250 mg) in dichloromethane (5 mL) at 0°C under nitrogen, was added *N,N*-dimethylformamide (1 drop) and oxalyl chloride (1 mL). The reaction mixture was stirred at room temperature for 1 hour, then evaporated to dryness and redissolved in dichloromethane (3 mL). This solution was cooled to 0°C and a
25 mixture of 5-quinolinamine (200 mg) and triethylamine (1 mL) in dichloromethane (2 mL) was added dropwise. The reaction mixture was stirred at room temperature for 1 hour then poured into saturated NaHCO_3 aq. (20 mL). The mixture was extracted with

dichloromethane (3×10 mL) and the combined extracts were dried, filtered and evaporated. Purification (SiO₂, ethyl acetate:*iso*hexane 3:2 as eluant) gave the title compound (30 mg).

¹H NMR (400 MHz, d₆-DMSO) δ 9.97 (1H, s), 8.92 (1H, dd), 8.45 (1H, m), 7.85 (1H, m),
5 7.79-7.70 (2H, m), 7.57 (1H, dd), 2.37 (2H, d), 1.92-1.58 (6H, m), 1.35-0.95 (5H, m).
MS: APCI(+ve) 269 (M+H⁺).
m.p. 183-184°C

Example 19

10 1-Methyl-*N*-5-quinolinyl-cyclohexaneacetamide



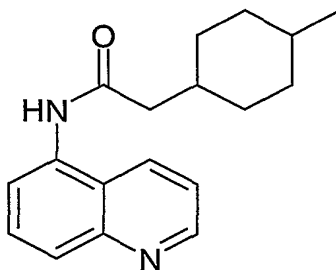
Prepared according to the method of example 18, using 5-quinolinamine (230 mg) and 1-methyl-cyclohexaneacetic acid (250 mg). Purification (SiO₂, methanol:dichloromethane 1:9 as eluant) followed by recrystallisation from methanol / ethyl acetate gave the title
15 compound as a colourless solid (80 mg).

¹H NMR (400 MHz, d₆-DMSO) δ 9.93 (1H, s), 8.91 (1H, dd), 8.45 (1H, d), 7.85 (1H, d),
7.78-7.70 (2H, m), 7.57 (1H, dd), 2.41 (2H, s), 1.60-1.30 (10H, m), 1.10 (3H, s).
MS: APCI(+ve) 283 (M+H⁺).
20 m.p. 133-135°C

Example 20

4-Methyl-*N*-5-quinolinyl-cyclohexaneacetamide

88



Prepared according to the method of example 18, using 5-quinolinamine (250 mg) and 4-methyl-cyclohexaneacetic acid (270 mg). Purification (HPLC, Symmetry - 0.1% aqueous trifluoroacetic acid / acetonitrile) followed by recrystallisation from methanol / ethyl acetate gave the title compound as a colourless solid (84 mg).

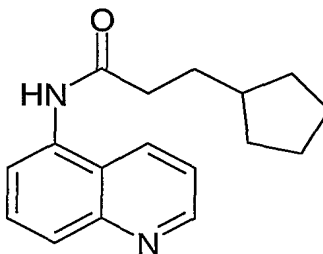
^1H NMR (300 MHz, d_6 -DMSO) δ 9.97 (1H, m), 8.80 (1H, dd), 8.44 (1H, d), 7.85 (1H, m), 7.80-7.68 (2H, m), 7.57 (1H, ddd), 2.50-2.35 (2H, m), 1.85-1.20 (6H, m), 1.17-0.90 (4H, m), 0.87 (3H, d).

MS: APCI(+ve) 283 ($\text{M}+\text{H}^+$).

m.p. 181-183°C

Example 21

N-5-Quinolinyl-cyclopentanepropanamide



Prepared according to the method of example 18, using 5-quinolinamine (250 mg) and cyclopentanepropanoic acid (270 mg). Purification (HPLC, Symmetry - 0.1% aqueous trifluoroacetic acid / acetonitrile) followed by recrystallisation from methanol / ethyl acetate gave the title compound as a colourless solid (112 mg).

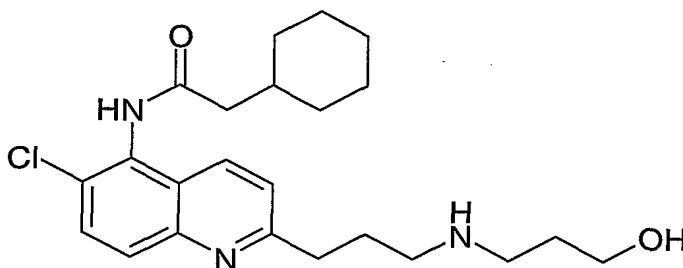
^1H NMR (400 MHz, d_6 -DMSO) δ 10.13 (1H, s), 9.05 (1H, dd), 8.71 (1H, d), 7.94-7.82 (3H, m), 7.74 (1H, dd), 2.53 (2H, m), 1.90-1.45 (9H, m), 1.15 (2H, m).

MS: APCI(+ve) 269 ($\text{M}+\text{H}^+$).

m.p. 135-138°C

Example 22

***N*-[6-Chloro-2-[3-[(3-hydroxypropyl)amino]propyl]-5-quinolinyl]-cyclohexaneacetamide**



a) [3-[(1,1-dimethylethyl)dimethylsilyl]oxy]propyl-2-propenyl-carbamic acid, 1,1-dimethylethyl ester

Prepared according to the method of example 15(b) using (2-bromopropoxy)-tert-butyl dimethylsilane.

MS: APCI(+ve) 230 ((M-boc)+H⁺).

b) *N*-[6-Chloro-2-[3-[(3-hydroxypropyl)amino]propyl]-5-quinolinyl]-cyclohexaneacetamide

Prepared according to the method of example 1(b)/(c), using *N*-(2,6-dichloro-5-quinolinyl)-cyclohexaneacetamide (Example 1(a)) (130 mg) and [3-[(1,1-dimethylethyl)dimethylsilyl]oxy]propyl-2-propenyl-carbamic acid, 1,1-dimethylethyl ester (example 22(a)) (152 mg). Purification (SiO₂, methanol:dichloromethane 1:9 as eluant) gave the title compound as a colourless solid (21 mg).

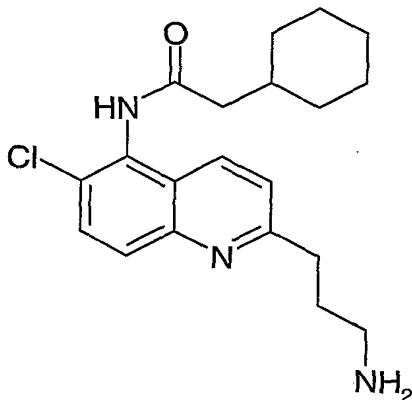
¹H NMR (400 MHz, CD₃OD) δ 8.12 (1H, d), 7.87 (1H, d), 7.74 (1H, d), 7.44 (1H, d), 3.60 (2H, t), 3.05-3.01 (6H, m), 2.36 (2H, d), 2.15-2.09 (2H, m), 1.84-1.78 (4H, m), 1.69 (2H, d), 1.62 (1H, d), 1.32-1.02 (6H, m).

MS: APCI(+ve) 418/420 (M+H⁺).

m.p. 159-163°C

Example 23

***N*-[2-(3-Aminopropyl)-6-chloro-5-quinolinyl]-cyclohexaneacetamide**



5

a) [3-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]propyl]-carbamic acid 1,1-dimethylethyl ester

To 2-propenyl-carbamic acid 1,1-dimethylethyl ester under nitrogen was added 9-borabicyclo[3.3.1]nonane (0.5M in tetrahydrofuran, 7.1 mL) and the mixture refluxed for 2 hours. The reaction was allowed to cool to room temperature and potassium phosphate (1.02 g) in water (1.8 mL) added. The resultant mixture was stirred for 15 minutes. *N*-(2,6-Dichloro-5-quinolinyl)-cyclohexaneacetamide (prepared as described in Example 1a) (0.5 g) was added followed by *tetrakis*(triphenylphosphine)palladium(0) (17 mg) in dimethylformamide (2.8 mL). The reaction was heated at 70°C under nitrogen for 4 hours. To the cooled solution was added brine (30 mL) and the mixture extracted with ethyl acetate (3x30 mL). The combined organics were dried, filtered and concentrated to give the sub-title compound (0.9 g).

MS: APCI(-ve) 458 (M-H⁺).

b) *N*-[2-(3-Aminopropyl)-6-chloro-5-quinolinyl]-cyclohexaneacetamide

Trifluoroacetic acid (5 mL) was added to a solution of [3-[6-chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]propyl]-carbamic acid, 1,1-dimethylethyl ester (Example 23(a)) (0.9 g) in dichloromethane (15 mL). After stirring for 2 hours the solvent

was removed under reduced pressure and the resulting residue was purified (Varian Chem elute cartridge with dichloromethane as eluant). Further purification (Varian SCX cartridge using methanol (100 mL) and then 10% ammonia in methanol (100 mL) as eluant) afforded the title compound (300 mg).

5

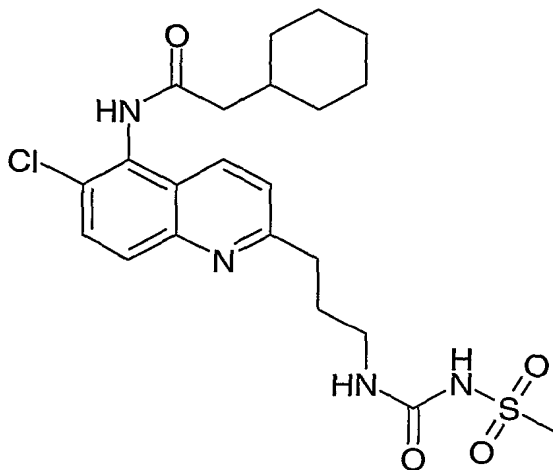
^1H NMR (400 MHz, CD_3OD) δ 8.21 (1H, d), 7.95 (1H, d), 7.82 (1H, d), 7.54 (1H, d), 3.04 (2H, t), 2.83 (2H, t), 2.46 (2H, d), 2.04 (2H, quint.), 1.99-1.89 (3H, m), 1.83-1.76 (2H, m), 1.75-1.68 (1H, m), 1.43-1.22 (3H, m), 1.21-1.09 (2H, m).

MS: APCI(+ve) 360 ($\text{M}+\text{H}^+$).

10 m.p. 121-130 °C

Example 24

***N*-[6-Chloro-2-[3-[[[(methylsulfonyl)amino]carbonyl]amino]propyl]-5-quinolinyl]-cyclohexaneacetamide**



15

To a stirred solution of *para*-nitrophenylchloroformate (0.050 g) in dichloromethane was added dimethylaminopyridine (0.031 g), the mixture was stirred under nitrogen for 5 minutes and then triethylamine (0.035 mL) and methanesulphonamide (0.024 g) were added. The reaction was stirred for 1 hour before *N*-[2-(3-aminopropyl)-6-chloro-5-quinolinyl]-cyclohexaneacetamide (Example 23 (b)) (0.080 g) was added and the mixture was stirred for 1 hour under nitrogen. The solvent was removed under reduced pressure and the residue purified (MAX Waters cartridge, using methanol (30 mL) and 10% acetic

20

acid in methanol (50 mL) as eluant). Removal of the solvent afforded the title compound (0.020 g).

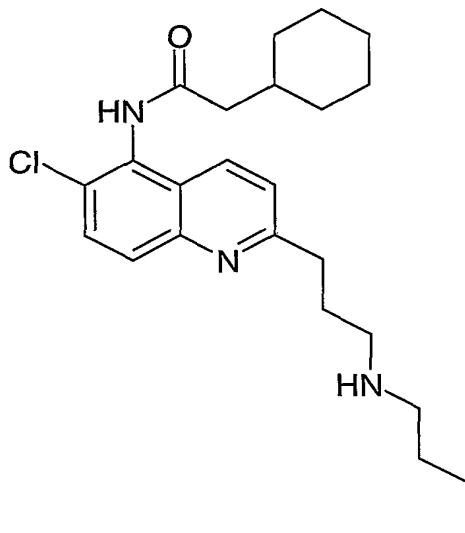
¹H NMR (400 MHz, CD₃OD) δ 8.31 (1H, d), 7.67 (2H, s), 7.42 (1H, d), 3.19 (2H, t), 2.99-2.92 (5H, m), 2.37-2.31 (2H, m), 2.02-1.88 (4H, m), 1.81-1.74 (2H, m), 1.73-1.66 (1H, m), 1.41-1.20 (4H, m), 1.20-1.06 (2H, m).

MS: APCI(-ve) 479 (M-H⁺).

m.p. 151-152°C

10 Example 25

***N*-[2-[3-(Butylamino)propyl]-6-chloro-5-quinolinyl]-cyclohexaneacetamide dihydrochloride**



A solution of *N*-[2-(3-aminopropyl)-6-chloro-5-quinolinyl]-cyclohexaneacetamide (0.2 g) (Example 23), acetic acid (1 drop) and butanal (0.074 mL) in tetrahydrofuran was placed in a 10 mL vial and heated at 100°C for 30 minutes within a microwave. Once the reaction had cooled to room temperature sodium triacetoxyborohydride (0.236 g) was added and the mixture stirred for 12 hours. The solvent was removed and the residue taken up in dimethylsulfoxide (3 mL). The residue was purified by HPLC (Waters Symmetry column using 25% to 95% acetonitrile in 0.1% aqueous trifluoroacetic acid). Further purification (SiO₂, ammonia: methanol: dichloromethane, 1:4:95 as eluant) followed by removal of

solvent and conversion to its hydrochloride salt with 4M hydrogen chloride in 1,4-dioxane (5 mL) afforded the title product (0.021 g).

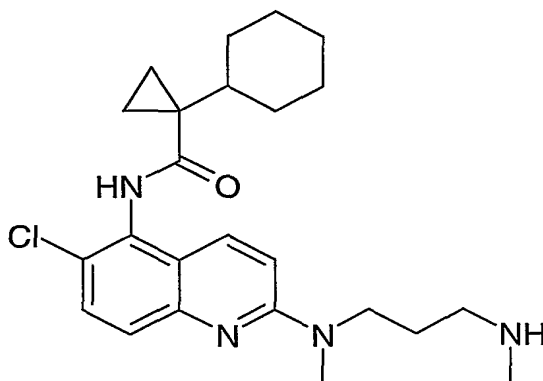
¹H NMR (400 MHz, d₆-DMSO) δ 10.08 (1H, s), 8.73 (2H, s), 8.25 (1H, d), 7.98 (1H, d), 7.89 (1H, d), 7.63 (1H, d), 3.08 (2H, t), 3.03-2.94 (2H, m), 2.93-2.84 (2H, m), 2.38 (2H, d), 2.16 (2H, quintet), 1.90-1.77 (3H, m), 1.76-1.68 (2H, m), 1.67-1.54 (3H, m), 1.38-1.14 (6H, m), 1.13-1.00 (2H, m), 0.89 (3H, t).

MS: APCI(+ve) 416 (M+H⁺).

m.p. 219-221°C

Example 26

***N*-[6-Chloro-2-[methyl[3-(methylamino)propyl]amino]-5-quinolinyl]-1-cyclohexyl-cyclopropanecarboxamide, hydrochloride**



a) 1-Cyclohexyl cyclopropanecarboxylic acid

To 1-phenyl-cyclopropanecarboxylic acid (0.500 g) in acetic acid (2 mL) was added Adams catalyst (0.050 g) in ethanol (0.3 mL). The reaction was left to stir for 48 hours under 5 bar of hydrogen. The reaction was filtered, washing with ethanol (10 mL) and water (10 mL). The resulting solid was collected by filtration and subsequently washed with water (10 mL) to afford the sub-titled compound (0.3 g).

¹H NMR (400 MHz, CD₃OD) δ 1.77-1.71 (2H, m), 1.68-1.62 (3H, m), 1.43-1.12 (6H, m), 1.07 (2H, q), 0.73 (2H, q).

MS: APCI(-ve) 167 (M-H⁺).

b) 1-Cyclohexyl-*N*-(2,6-dichloro-5-quinolinyl)-cyclopropanecarboxamide

Prepared according to the method of example 1(a), using 2,6-dichloro-5-quinolinamine (prepared as described in Example 1(d)) (0.3 g) and 1-cyclohexyl cyclopropanecarboxylic acid (Example 26(a)) (0.28 g) at 100°C for 15 hours. Purification by chromatography (SiO₂, dichloromethane as eluant) afforded the sub-title compound (0.26 g).

¹H NMR (400 MHz, CD₃OD) δ 8.15 (1H, d), 7.91 (1H, d), 7.87 (1H, d), 7.59 (1H, d), 1.95-1.88 (2H, m), 1.87-1.75 (2H, m), 1.74-1.68 (1H, m), 1.42-1.17 (6H, m), 1.14 (2H, dd), 0.89 (2H, dd).

MS: APCI(-ve) 361 (M-H⁺).

c) *N*-[6-Chloro-2-[methyl[3-(methylamino)propyl]amino]-5-quinolinyl]-1-cyclohexyl-cyclopropanecarboxamide, hydrochloride

To a 10 mL vial was added 1-cyclohexyl-*N*-(2,6-dichloro-5-quinolinyl)-

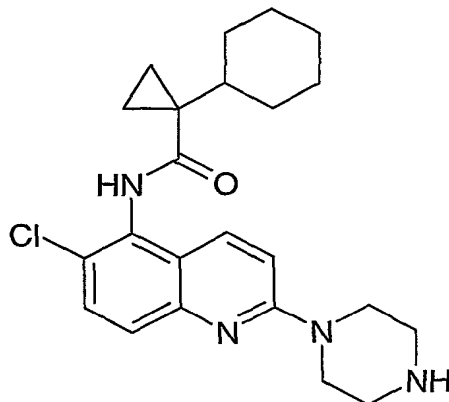
cyclopropanecarboxamide (example 26 (b)) (0.13 g), *N,N'*-dimethyl-1,3-propanediamine (0.13 mL) and acetonitrile (3 mL). The vial was sealed and heated at 100°C in a microwave for 20 minutes followed by 30 minutes at 110°C. The solvent was removed from the cooled reaction under reduced pressure, saturated aqueous sodium hydrogen carbonate solution (30 mL) was added and the mixture was extracted with dichloromethane (3 x 50 mL). The combined organics were washed with water (50 mL) and brine (50 mL) before being dried, filtered and concentrated. Purification (Varian SCX cartridge, using methanol and 10% ammonia in methanol as eluant) gave a crude product which was further purified by chromatography (SiO₂, ammonia: methanol: dichloromethane, 1:2.5:96.5 as eluant). The product was converted to its hydrochloride salt by dissolution in dichloromethane and treatment with 4M hydrogen chloride in 1,4-dioxane (5 mL). Removal of volatiles and recrystallisation from methanol / acetonitrile afforded the title compound (0.075 g).

¹H NMR (400 MHz, CD₃OD) δ 8.03 (1H, d), 7.94 (1H, s), 7.81 (1H, d), 7.47 (1H, d), 3.86 (2H, t), 3.38 (3H, s), 3.06 (2H, t), 2.65 (3H, s), 2.06 (2H, quint.), 1.80 (2H, d), 1.76-1.65 (2H, m), 1.62 (2H, d), 1.33-1.19 (3H, m), 1.18-1.06 (2H, m), 1.04 (2H, dd), 0.82 (2H, dd). MS: APCI(+ve) 428 (M+H⁺).

m.p. 215-218°C

Example 27

N-[6-Chloro-2-(1-piperazinyl)-5-quinolinyl]-1-cyclohexyl-cyclopropanecarboxamide



5

To a 10 mL vial was added 1-cyclohexyl-*N*-(2,6-dichloro-5-quinolinyl)-cyclopropanecarboxamide (Example 26 (b)) (0.13 g), piperazine (0.091 g) and acetonitrile (3 mL). The vial was sealed and heated in a microwave at 110°C for 40 minutes. The solvent was removed from the cooled reaction and the residue taken up in dichloromethane and purified (SiO₂, ammonia: methanol: dichloromethane, 1:2:97 as eluant). The solvent was removed from the combined fractions and the product recrystallised from ethanol to afford the title compound (0.050 g).

10

¹H NMR (400 MHz, CD₃OD) δ 7.77 (1H, d), 7.48 (2H, d), 7.12 (1H, d), 3.63 (4H, t), 2.83 (4H, t), 1.85-1.78 (2H, m), 1.76-1.69 (2H, m), 1.66-1.58 (2H, m), 1.31-1.04 (5H, m), 1.00 (2H, dd), 0.77-0.73 (2H, m).

15

MS: APCI(+ve) 413 (M+H⁺).

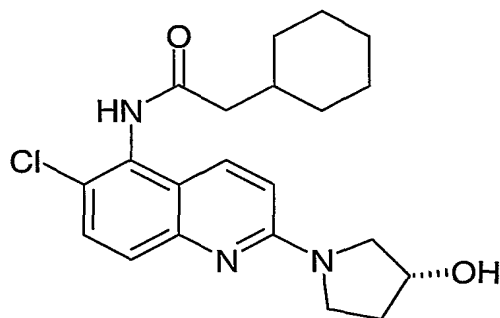
m.p. 219°C

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Example 28

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide

96



Prepared according to the method of example 27, using *N*-(2,6-dichloro-5-quinolinyl)-cyclohexaneacetamide (Example 1(a)) (0.05 g) and (3*R*)-3-pyrrolidinol (0.052 g) to afford the title compound (0.01 g).

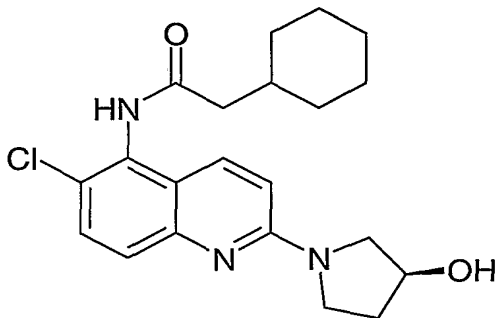
¹H NMR (400 MHz, d₆-DMSO) δ 9.76 (1H, s), 7.84 (1H, d), 7.51 (2H, dd), 6.95 (1H, d), 5.01-4.97 (1H, m), 4.42 (1H, s), 3.67-3.53 (3H, m), 3.52-3.42 (1H, m), 2.32 (2H, d), 2.09-1.98 (1H, m), 1.97-1.88 (1H, m), 1.87-1.77 (3H, m), 1.75-1.67 (2H, m), 1.67-1.60 (1H, m), 1.33-1.12 (3H, m), 1.11-0.99 (2H, m).

MS: APCI(+ve) 388 (M+H⁺).

m.p. 226-227°C

Example 29

N-[6-Chloro-2-[(3*S*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide



Prepared according to the method of example 27, using *N*-(2,6-dichloro-5-quinolinyl)-cyclohexaneacetamide (Example 1(a)) (0.533 g) and (3*S*)-3-pyrrolidinol (0.365 g) to afford the title compound (0.48 g).

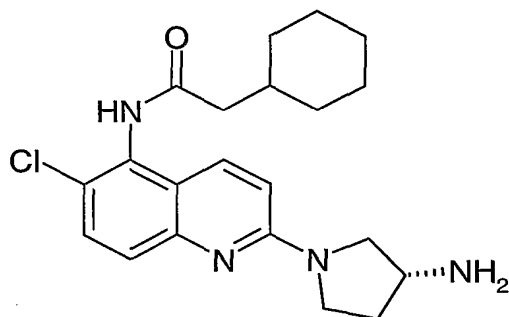
^1H NMR (400 MHz, $\text{d}_6\text{-DMSO}$) δ 9.76 (1H, s), 7.84 (1H, d), 7.54 (1H, d), 7.47 (1H, d), 6.94 (1H, d), 5.02-4.96 (1H, m), 4.42 (1H, s), 3.69-3.53 (3H, m), 3.52-3.41 (1H, m), 2.32 (2H, d), 2.10-1.99 (1H, m), 1.98-1.88 (1H, m), 1.87-1.76 (3H, m), 1.75-1.67 (2H, m), 1.67-1.60 (1H, m), 1.33-1.13 (3H, m), 1.12-0.99 (2H, m).

5 MS: APCI(+ve) 388 ($\text{M}+\text{H}^+$).

m.p. 219-221°C

Example 30

N-[2-[(3*R*)-3-Amino-1-pyrrolidinyl]-6-chloro-5-quinolinyl]-cyclohexaneacetamide



10

To a 10 mL vial was added *N*-(2,6-dichloro-5-quinolinyl)-cyclohexaneacetamide (Example 1(a)) (0.166 g), (3*R*)-3-pyrrolidinamine (0.127 g), triethylamine (0.083 mL) and acetonitrile (5 mL). The vial was sealed and heated at 100°C for 30 minutes within a microwave. The reaction was cooled to room temperature and the resulting solid removed by filtration. This solid was purified (Varian SCX cartridge, using methanol and 10% ammonia in methanol as eluant) to afford the title compound (0.102 g).

15

^1H NMR (400 MHz, $\text{d}_6\text{-DMSO}$) δ 9.75 (1H, s), 7.83 (1H, d), 7.54 (1H, d), 7.46 (1H, d), 6.92 (1H, d), 3.70-3.48 (4H, m), 3.26-3.18 (1H, m), 2.32 (2H, d), 2.11-2.02 (1H, m), 1.89-1.60 (9H, m), 1.33-1.13 (3H, m), 1.11-0.97 (2H, m).

20

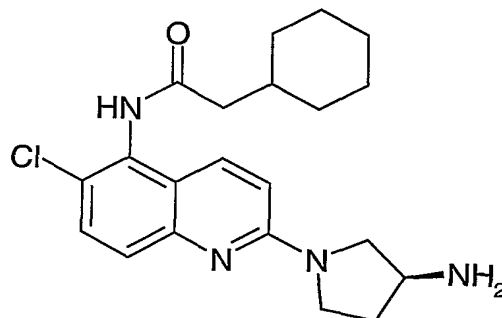
MS: APCI(+ve) 387 ($\text{M}+\text{H}^+$).

m.p. 201-206°C

Example 31

25 *N*-[2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-chloro-5-quinolinyl]-cyclohexaneacetamide

98



Prepared according to the method of example 30, using *N*-(2,6-dichloro-5-quinolinyl)-cyclohexanecarboxamide (Example 1(a)) (0.166 g) and (3*S*)-3-pyrrolidinamine (0.127 g) to afford the title compound (0.113 g).

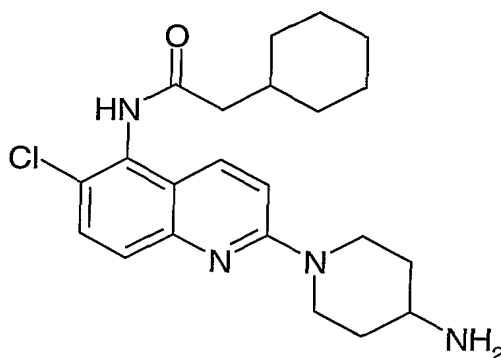
5

¹H NMR (400 MHz, d₆-DMSO) δ 9.76 (1H, s), 7.84 (1H, d), 7.54 (1H, d), 7.46 (1H, d), 6.93 (1H, d), 3.70-3.58 (3H, m), 3.58-3.49 (1H, m), 3.28-3.21 (1H, m), 2.32 (2H, d), 2.14-2.04 (1H, m), 1.88-1.76 (4H, m), 1.76-1.67 (4H, m), 1.67-1.60 (1H, m), 1.32-1.11 (3H, m), 1.11-0.99 (2H, m).

10 MS: APCI(+ve) 387 (M+H⁺).
m.p. 219-226°C

Example 32

***N*-[2-(4-Amino-1-piperidinyl)-6-chloro-5-quinolinyl]-cyclohexanecarboxamide**



15

Prepared according to the method of example 30, using *N*-(2,6-dichloro-5-quinolinyl)-cyclohexanecarboxamide (Example 1(a)) (0.113 g) and 4-piperidinamine (0.152 mL) to afford the title compound (0.109 g).

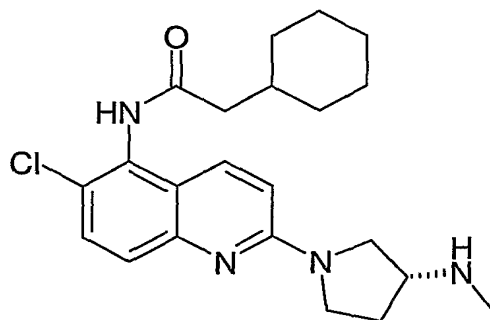
¹H NMR (400 MHz, d₆-DMSO) δ 9.82 (1H, s), 7.87 (1H, d), 7.59 (1H, d), 7.49 (1H, d), 7.35 (1H, d), 4.57-4.49 (2H, m), 3.27-3.18 (2H, m), 3.08-2.99 (3H, m), 2.35-2.31 (2H, m), 1.97-1.90 (2H, m), 1.84-1.77 (4H, m), 1.75-1.67 (2H, m), 1.67-1.61 (1H, m), 1.48-1.33 (3H, m), 1.32-1.15 (2H, m), 1.11-0.99 (1H, m).

5 MS: APCI(+ve) 401 (M+H⁺).

m.p. 333-334°C

Example 33

N-[6-Chloro-2-[(3*R*)-3-(methylamino)-1-pyrrolidinyl]-5-quinolinyl]-
10 cyclohexaneacetamide



a) *N*-[6-Chloro-2-[(3*S*)-3-[(methylsulfonyl)oxy]-1-pyrrolidinyl]-5-quinolinyl]-
cyclohexaneacetamide

To a stirred solution of *N*-[6-chloro-2-[(3*S*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-
15 cyclohexaneacetamide (Example 29) (0.4 g) in dichloromethane was added
methanesulphonyl chloride (0.104 mL) and triethylamine (0.215 mL). The reaction was
stirred for 12 hours under nitrogen and then purified (Varian Chem elute cartridge,
saturated sodium hydrogen carbonate solution and dichloromethane as eluant) to afford the
sub-title compound (0.45 g).

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MS: APCI(+ve) 466 (M+H⁺).

b) *N*-[6-Chloro-2-[(3*R*)-3-(methylamino)-1-pyrrolidinyl]-5-quinolinyl]-
cyclohexaneacetamide

25 To a 10 mL vial was added *N*-[6-Chloro-2-[(3*S*)-3-[(methylsulfonyl)oxy]-1-pyrrolidinyl]-
5-quinolinyl]-cyclohexaneacetamide (Example 33(a)) (225 mg) and 8M methylamine in

ethanol (6 mL). The vial was sealed and heated at 80°C for 120 minutes within a microwave. The solvent was removed under vacuum and purified (SiO₂, ammonia: methanol: dichloromethane, 1:2:97 as eluant) to afford the titled compound (0.033 g).

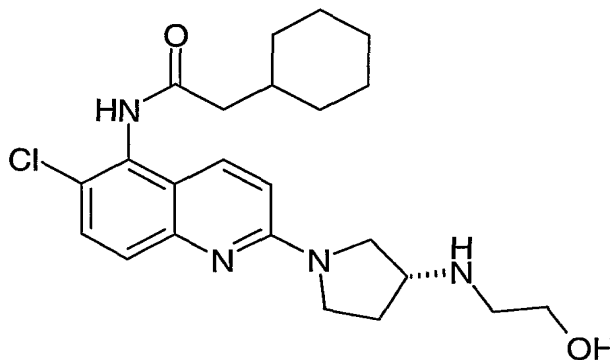
5 ¹H NMR (400 MHz, d₆-DMSO) δ 9.75 (1H, s), 7.83 (1H, d), 7.54 (1H, d), 7.46 (1H, d), 6.93 (1H, d), 3.69-3.63 (1H, m), 3.63-3.48 (2H, m), 3.36-3.23 (4H, m), 2.30 (3H, s), 2.14-2.04 (1H, m), 1.89-1.75 (4H, m), 1.75-1.67 (2H, m), 1.67-1.59 (1H, m), 1.32-1.12 (3H, m), 1.11-0.97 (2H, m).

MS: APCI(+ve) 401 (M+H⁺).

10 m.p. 169°C

Example 34

***N*-[6-Chloro-2-[(3*R*)-3-[(2-hydroxyethyl)amino]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide**



15

Prepared according to the method of example 33(b), using *N*-[6-Chloro-2-[(3*S*)-3-[(methylsulfonyl)oxy]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide (Example 33(a)) (0.225 g) and ethanolamine (2 mL) to afford the title compound (0.052 g).

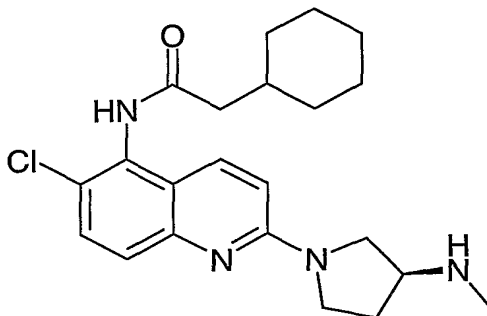
20 ¹H NMR (400 MHz, d₆-DMSO) δ 9.75 (1H, s), 7.83 (1H, d), 7.54 (1H, d), 7.46 (1H, d), 6.93 (1H, d), 3.72-3.66 (1H, m), 3.66-3.57 (1H, m), 3.57-3.49 (1H, m), 3.48-3.44 (2H, m), 3.42-3.36 (2H, m), 2.69-2.59 (2H, m), 2.32 (2H, d), 2.16-2.07 (1H, m), 1.88-1.76 (4H, m), 1.75-1.67 (2H, m), 1.67-1.60 (1H, m), 1.33-1.13 (3H, m), 1.10-0.99 (2H, m).

MS: APCI(+ve) 431 (M+H⁺).

25 m.p. 197-199°C

Example 35

***N*-[6-Chloro-2-[(3*S*)-3-(methylamino)-1-pyrrolidinyl]-5-quinoliny]-cyclohexaneacetamide**



a) *N*-[6-Chloro-2-[(3*R*)-3-[(methylsulfonyl)oxy]-1-pyrrolidinyl]-5-quinoliny]-cyclohexaneacetamide

Prepared according to the method of example 33(a), using *N*-[6-chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinoliny]-cyclohexaneacetamide (Example 28) (0.46 g) and methanesulphonyl chloride (0.183 mL) to afford the sub-title compound (0.47 g).

MS: APCI(+ve) 466 ($M+H^+$).

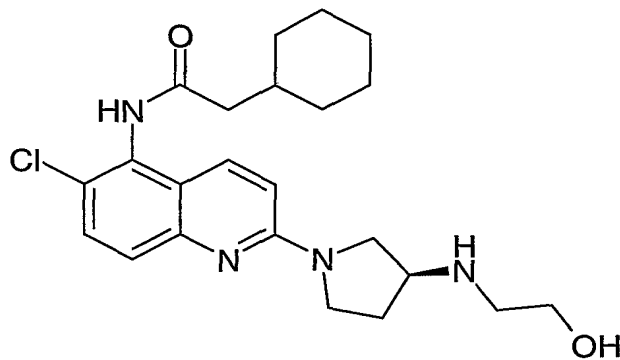
b) *N*-[6-Chloro-2-[(3*S*)-3-(methylamino)-1-pyrrolidinyl]-5-quinoliny]-cyclohexaneacetamide

Prepared according to the method of example 33(b), using *N*-[6-Chloro-2-[(3*R*)-3-[(methylsulfonyl)oxy]-1-pyrrolidinyl]-5-quinoliny]-cyclohexaneacetamide (Example 35(a)) (0.2 g) and 8M methylamine in ethanol (3 mL) to afford the title compound (0.063 g).

^1H NMR (400 MHz, d_6 -DMSO) δ 9.75 (1H, s), 7.83 (1H, d), 7.54 (1H, d), 7.46 (1H, d), 6.93 (1H, d), 3.66 (1H, dd), 3.63-3.48 (2H, m), 3.4-3.22 (4H, m), 2.31 (3H, s), 2.15-2.04 (1H, m), 1.88-1.76 (4H, m), 1.75-1.67 (2H, m), 1.67-1.60 (1H, m), 1.32-1.12 (3H, m), 1.10-0.99 (2H, m).

MS: APCI(+ve) 401 ($M+H^+$).

m.p. 164-165°C

Example 36***N*-[6-Chloro-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide**

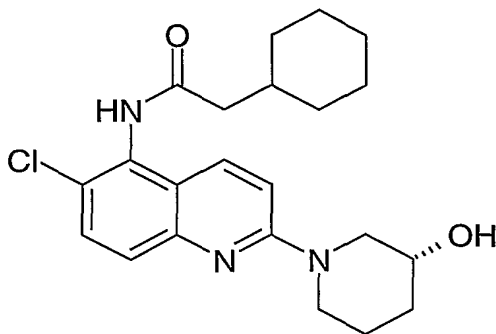
5

Prepared according to the method of example 33(b), using *N*-[6-Chloro-2-[(3*R*)-3-[(methylsulfonyl)oxy]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide (Example 35(a)) (0.2 g) and ethanolamine (0.8 mL) to afford the title compound (0.068 g).

10 ^1H NMR (400 MHz, $\text{d}_6\text{-DMSO}$) δ 9.75 (1H, s), 7.83 (1H, d), 7.54 (1H, d), 7.46 (1H, d), 6.93 (1H, d), 4.48 (1H, t), 3.72-3.57 (2H, m), 3.56-3.49 (1H, m), 3.49-3.36 (4H, m), 2.68-2.62 (2H, m), 2.32 (2H, d), 2.17-2.07 (1H, m), 1.87-1.77 (4H, m), 1.75-1.67 (2H, m), 1.67-1.60 (1H, m), 1.33-1.12 (3H, m), 1.10-0.98 (2H, m).

MS: APCI(+ve) 431 ($\text{M}+\text{H}^+$).

15 m.p. 194-196°C

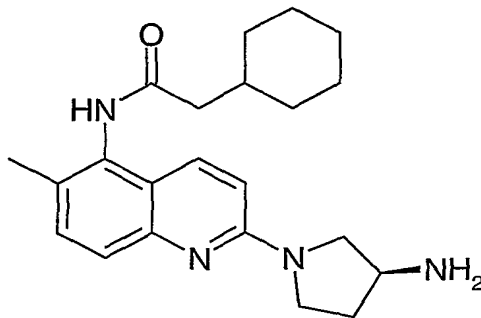
Example 37***N*-[6-Chloro-2-[(3*R*)-3-hydroxy-1-piperidinyl]-5-quinolinyl]-cyclohexaneacetamide**

N-(2,6-Dichloro-5-quinolinyl)-cyclohexaneacetamide (Example 1(a)) (1 g), (3*R*)-3-piperidinol hydrochloride (0.424 g) and triethylamine (1.2 mL) were placed into a 10 mL microwave vial followed by the addition of acetonitrile (3 mL). The vial was sealed and heated at 120 °C in a single mode microwave for 45 minutes. On cooling a solid crystallised from the reaction mixture which was filtered and washed with acetonitrile (10 mL) to afford the sub-title compound (0.7 g).

¹H NMR (400 MHz, d₆-DMSO) δ 9.77 (1H, s), 7.83 (1H, d), 7.56 (1H, d), 7.46 (1H, d), 7.29 (1H, d), 4.89 (1H, s), 4.33 (1H, d), 4.12 (1H, d), 3.52 (1H, s), 3.21-3.11 (1H, m), 2.94 (1H, t), 2.32 (2H, d), 1.96-1.88 (1H, m), 1.87-1.75 (4H, m), 1.75-1.67 (2H, m), 1.67-1.59 (1H, m), 1.50-1.38 (2H, m), 1.33-1.11 (3H, m), 1.10-0.98 (2H, m).
MS: APCI(+ve) 402 (M+H⁺).
m.p. 209-214°C

15 Example 38

N-[2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-methyl-5-quinolinyl]-cyclohexaneacetamide



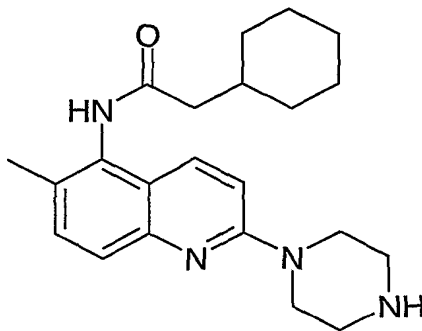
Prepared according to the method of example 30, using *N*-(2-Chloro-6-methyl-5-quinolinyl)-cyclohexaneacetamide (Example 15(a)) (0.2 g) and (3*S*)-3-pyrrolidinamine (0.163 g) which after recrystallisation from ethanol afforded the title compound (0.159 g).

¹H NMR (400 MHz, d₆-DMSO) δ 9.53 (1H, s), 7.85 (1H, d), 7.42-7.32 (2H, m), 6.83 (1H, d), 3.69-3.56 (3H, m), 3.55-3.40 (2H, m), 3.25-3.18 (1H, m), 2.31 (2H, d), 2.20 (3H, s), 2.12-2.03 (1H, m), 1.88-1.60 (8H, m), 1.33-1.13 (3H, m), 1.11-0.98 (2H, m).
MS: APCI(+ve) 367 (M+H⁺).

m.p. 223-224°C

Example 39

N-[6-Methyl-2-(1-piperazinyl)-5-quinolinyl]-cyclohexaneacetamide



5

Prepared according to the method of example 2, using *N*-(2-Chloro-6-methyl-5-quinolinyl)-cyclohexaneacetamide (Example 15(a)) (0.2 g) and piperazine (0.163 g). The reaction was cooled to room temperature, the resulting solid collected by filtration and recrystallised from methanol to afford the title compound (0.102 g).

10

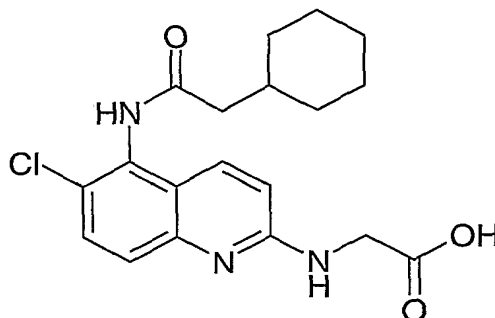
¹H NMR (400 MHz, CD₃OD/TFA) δ 8.35 (1H, d), 7.81 (2H, dd), 7.54 (1H, d), 4.25-4.14 (4H, m), 3.56-3.46 (4H, m), 2.46 (2H, d), 2.40 (3H, s), 1.99 - 1.67 (6H, m), 1.43-1.08 (5H, m).

MS: APCI(+ve) 367 (M+H⁺).

15

Example 40

N-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-glycine



20

a) *N*-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-glycine, 1,1-dimethylethyl ester

Prepared according to the method of example 7 (a), using *N*-(2,6-dichloro-5-quinolinyl)-cyclohexaneacetamide (Example 1 (a)) (400 mg) and glycine *tert*-butyl ester hydrochloride (1.5 g) to afford the sub-title compound (63 mg).

MS: APCI(+ve) 432/434 ($M+H^+$).

b) *N*-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-glycine

Prepared according to the method of example 7 (b), using *N*-[6-chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-glycine, 1,1-dimethylethyl ester (Example 40(a)) (63 mg) and trifluoroacetic acid (2 mL). Purification by HPLC (Symmetry - 0.1% aqueous ammonium acetate / acetonitrile) afforded the title product (27 mg).

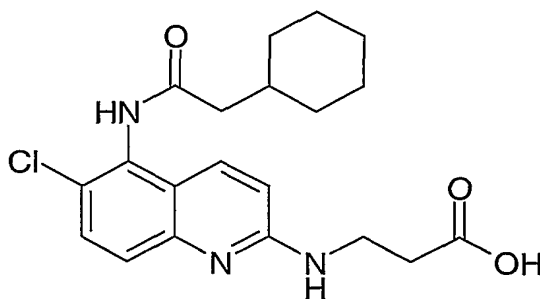
1H NMR (400 MHz, d_6 -DMSO) δ 9.42 (1H, br s), 7.77 (1H, d), 7.50 (1H, d), 7.42 (1H, d), 7.09 (1H, br s), 6.92 (1H, d), 4.08 (2H, br s), 2.31 (2H, br m), 1.91-1.59 (6H, m), 1.34-1.00 (5H, m).

MS: APCI(-ve) 374/376 ($M-H^+$).

m.p. 222-225°C dec.

Example 41

***N*-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]- β -alanine**



a) *N*-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]- β -alanine, 1,1-dimethylethyl ester

Prepared according to the method of example 7 (a), using *N*-(2,6-dichloro-5-quinolinyl)-cyclohexaneacetamide (Example 1 (a)) (400 mg) and β -alanine *tert*-butyl ester

5 hydrochloride (1.6 g) to afford the sub-title compound (150 mg).

MS: APCI(+ve) 446/448 ($M+H^+$).

b) *N*-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]- β -alanine

10 Prepared according to the method of example 7 (b), using *N*-[6-chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]- β -alanine, 1,1-dimethylethyl ester (Example 41 (a)) (150 mg) and trifluoroacetic acid (2 mL). Purification by HPLC (Symmetry - 0.1% aqueous ammonium acetate / acetonitrile) afforded the title product (39 mg).

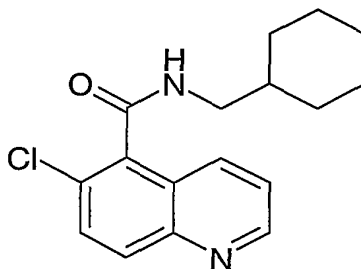
1H NMR (400 MHz, d_6 -DMSO) δ 12.23 (1H, s), 9.73 (1H, s), 7.71 (1H, d), 7.53 (1H, d),
15 7.45 (1H, d), 7.27 (1H, t), 6.82 (1H, d), 3.59 (2H, td), 2.58 (2H, t), 2.31 (2H, d), 1.89-1.59 (6H, m), 0.97-1.33 (5H, m).

MS: APCI(-ve) 388/390 ($M-H^+$).

m.p. 222-224°C dec.

20 Example 42

6-Chloro-*N*-(cyclohexylmethyl)quinoline-5-carboxamide



To a solution of 5-bromo-6-chloroquinoline (prepared according to the method of Journal
25 of Heterocyclic Chemistry 1967, 4, 410) (4.0 g), cyclohexanemethylamine (4.2 mL) and triethylamine (2.4 mL) in *N*-methyl pyrrolidinone (40 mL) was added dichlorobis(triphenylphosphine)palladium(II) (1.6 g). The mixture was heated with stirring

at 100°C under a 6 bar pressure of carbon monoxide for 18 hours after which it was cooled and filtered through diatomaceous earth, washing with methanol. The combined organics were concentrated to give a residue which was purified (SiO₂, *iso*hexane:ethyl acetate: ammonia in methanol (7 M) 49:49:2 as eluant) to yield the title compound as a solid (4.6 g).

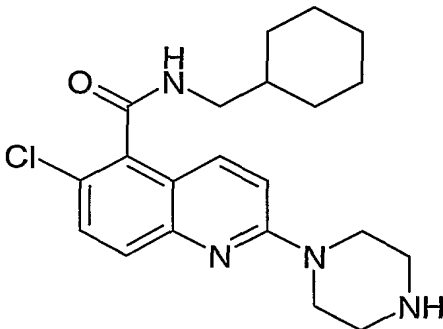
¹H NMR (300 MHz, d₆-DMSO) δ 8.97 (1H, dd), 8.75 (1H, t), 8.10 (1H, dd), 8.07 (1H, d), 7.82 (1H, d), 7.65 (1H, dd), 3.21 (2H, dd), 1.50-1.86 (6H, m), 0.91-1.32 (5H, m).

MS: APCI(+ve) 303/305 (M+H⁺).

m.p. 193-194°C

Example 43

6-Chloro-*N*-(cyclohexylmethyl)-2-(1-piperazinyl)-5-quinolinecarboxamide, dihydrochloride



a) 2,6-Dichloro-*N*-(cyclohexylmethyl)quinoline-5-carboxamide

To a solution of 6-chloro-*N*-(cyclohexylmethyl)quinoline-5-carboxamide (Example 42) (1.0 g) was added a mixture of aqueous hydrogen peroxide (5 mL, 27 %) and glacial acetic acid (8 mL) over 10 minutes. The mixture was heated with stirring at 65°C for 3 hours after which it was cooled to room temperature and partitioned between dichloromethane and water. The organic layer was separated and the aqueous layer was further extracted with dichloromethane. The combined organic extracts were washed with aqueous saturated sodium bicarbonate before being dried, filtered and evaporated to give a residue to which phosphorous oxychloride (5 mL) was added over 10 minutes. The mixture was heated

with stirring at 120°C under an atmosphere of nitrogen for 3 hours after which it was cooled to room temperature and the volatile components were removed *in vacuo* to leave a residue which was partitioned between dichloromethane and water. The organic layer was separated, the aqueous layer was further extracted with dichloromethane and the combined
5 organic extracts were washed with aqueous saturated sodium bicarbonate before being dried, filtered and evaporated to yield the sub-titled compound as a solid (0.90 g).

MS: APCI(+ve) 337/339 (M+H⁺).

10

b) 6-Chloro-*N*-(cyclohexylmethyl)-2-(1-piperazinyl)-5-quinolinecarboxamide, dihydrochloride

A stirred solution of 2,6-dichloro-*N*-(cyclohexylmethyl)quinoline-5-carboxamide (Example 43 (a)) (200 mg) and piperazine (160 mg) in acetonitrile (2 mL) was heated at
15 80°C in a CEM Discover microwave for 1 hour after which it was cooled to room temperature and concentrated. The residue was purified (Waters' SCX resin, ammonia in methanol (7 M) as eluant) and the resultant product was converted to the dihydrochloride salt by treatment with hydrochloric acid (4M in 1,4-dioxane). Recrystallisation (methanol / ethyl acetate) afforded the title compound as a solid (110 mg).

20

¹H NMR (300 MHz, d₆-DMSO) δ 9.35 (1H, br s), 8.72 (1H, t), 7.87 (1H, d), 7.75 (1H, br d), 7.65 (1H, d), 7.46 (1H, d), 4.00 (4H, br s), 3.23-3.19 (6H, m), 1.81-1.65 (6H, m), 1.24-0.92 (5H, m).

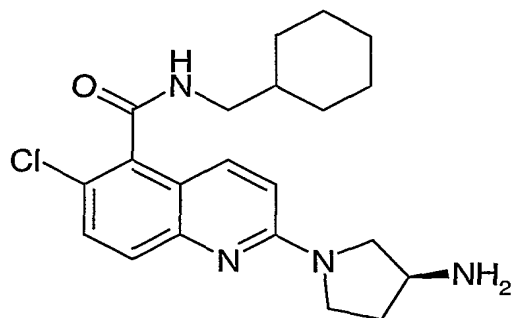
MS: APCI(+ve) 387/389 (M+H⁺).

25 m.p. 305-306°C.

Example 44

2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-chloro-*N*-(cyclohexylmethyl)-5-quinolinecarboxamide

109

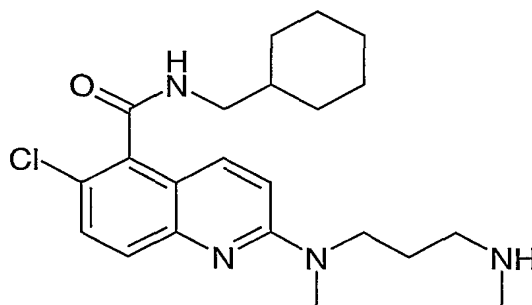


A stirred suspension of 2,6-dichloro-*N*-(cyclohexylmethyl)quinoline-5-carboxamide (Example 43(a)) (500 mg) and (3*S*)-3-pyrrolidinamine (0.60 mL) in acetonitrile (3 mL) was heated at 100°C in a microwave for 40 minutes after which it was cooled to room temperature and concentrated. Purification by chromatography (SiO₂, dichloromethane: methanol: ammonia in methanol (7 M) 95:5:0.5 as eluant) and subsequent recrystallisation (acetonitrile) afforded the title compound as a solid (280 mg).

- ¹H NMR (400 MHz, d₆-DMSO, 90°C) δ 8.26 (1H, br s), 7.74 (1H, d), 7.51 (1H, d), 7.44 (1H, d), 6.90 (1H, d), 3.72-3.59 (3H, m), 3.58-3.49 (1H, m), 3.26-3.16 (3H, m), 2.15-2.06 (1H, m), 1.83-1.56 (7H, m), 1.30-1.12 (3H, m), 1.08-0.96 (2H, m).
MS: APCI(+ve) 387/389 (M+H⁺).

15 Example 45

6-Chloro-*N*-(cyclohexylmethyl)-2-[methyl[3-(methylamino)propyl]amino]-5-quinoline carboxamide, dihydrochloride



- A stirred suspension of 2,6-dichloro-*N*-(cyclohexylmethyl)quinoline-5-carboxamide (Example 43 (a)) (250 mg) and *N,N'*-dimethyl-1,3-propanediamine (0.80 mL) in

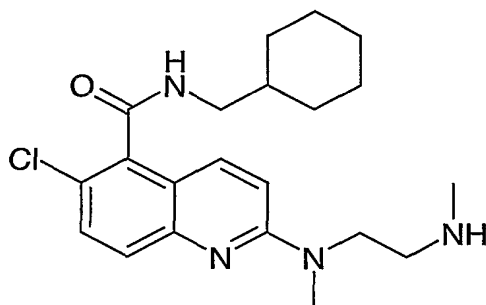
acetonitrile (3 mL) was heated at 100°C in a microwave for 2 hours after which it was cooled to room temperature and concentrated. The residue was purified by recrystallisation (methanol:ethyl acetate). The resultant product was converted to the dihydrochloride salt by treatment with hydrochloric acid (4M in 1,4-dioxane). Recrystallisation (methanol / ethyl acetate) afforded the title compound as a solid (110 mg).

¹H NMR (400 MHz, d₆-DMSO, 90°C) δ 9.09 (2H, br), 8.44 (1H, br), 8.07 (1H, br), 7.88 (1H, d), 7.64 (1H, d), 7.39 (1H, d), 3.90 (2H, t), 3.30 (3H, s), 3.22-3.19 (2H, m), 3.01-2.92 (2H, m), 2.55-2.50 (3H, m), 2.08-2.00 (2H, quin), 1.83-1.54 (6H, m), 1.31-0.97 (5H, m).

MS: APCI(+ve) 403/405 (M+H⁺).

Example 46

6-Chloro-*N*-(cyclohexylmethyl)-2-[methyl[2-(methylamino)ethyl]amino]-5-quinolinecarboxamide, dihydrochloride



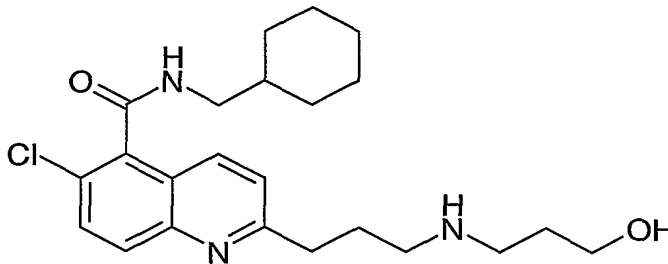
A stirred suspension of 2,6-dichloro-*N*-(cyclohexylmethyl)quinoline-5-carboxamide (Example 43 (a)) (200 mg) and *N,N'*-dimethyl-1,2-ethanediamine (0.30 mL) in acetonitrile (2 mL) was heated at 100°C in a microwave for 90 minutes after which it was cooled to room temperature and concentrated. Purification (SiO₂, dichloromethane: methanol: ammonia in methanol (7 M) 95:5:0.5), conversion to the dihydrochloride salt by treatment with hydrochloric acid (4M in 1,4-dioxane) and recrystallisation (methanol / ethyl acetate) afforded the title compound as a solid (160 mg).

¹H NMR (400 MHz, d₆-DMSO, 90°C) δ 9.23 (2H, br), 8.42 (1H, br), 7.95 (1H, br d), 7.88 (1H, d), 7.62 (1H, d), 7.39 (1H, d), 4.09 (2H, t), 3.28 (3H, s), 3.22-3.19 (4H, m), 2.59 (3H, s), 1.83-1.55 (6H, m), 1.31-0.96 (5H, m).

MS: APCI(+ve) 389/391 ($M+H^+$).

Example 47

6-Chloro-*N*-(cyclohexylmethyl)-2-[3-[(3-hydroxypropyl)amino]propyl]-5-quinolinecarboxamide



10 a) [3-[6-Chloro-5-[(cyclohexylmethyl)amino]carbonyl]-2-quinoliny]propyl][3-[(1,1-dimethylethyl)dimethylsilyl]oxy]propyl]-carbamic acid, 1,1-dimethyl ester

Prepared according to the method of Example 1(b), using 2,6-dichloro-*N*-(cyclohexylmethyl)quinoline-5-carboxamide (Example 43 (a)) (300 mg) and [3-[(1,1-dimethylethyl)dimethylsilyl]oxy]propyl]2-propenyl-carbamic acid, 1,1-dimethylethyl ester (Example 22(a)) (600 mg). Purification (SiO_2 , methanol: dichloromethane 1:9) gave the title compound as a colourless oil (510 mg).

MS: APCI(+ve) 633/635 ($M+H^+$).

20 b) 6-Chloro-*N*-(cyclohexylmethyl)-2-[3-[(3-hydroxypropyl)amino]propyl]-5-quinolinecarboxamide

HCl in 1,4-dioxane (4M, 3 mL) was added to 3-[6-chloro-5-[(cyclohexylmethyl)amino]carbonyl]-2-quinoliny]propyl][3-[(1,1-dimethylethyl)dimethylsilyl]oxy]propyl]-carbamic acid, 1,1-dimethyl ester (Example 47(a)) (500 mg) and the mixture was stirred for 4 hours at room temperature before being concentrated. Purification (SiO_2 , dichloromethane: methanol: ammonia in methanol (7 M) 97:3:0.5) and recrystallisation (methanol / ethyl acetate) afforded the title compound as a solid (90 mg).

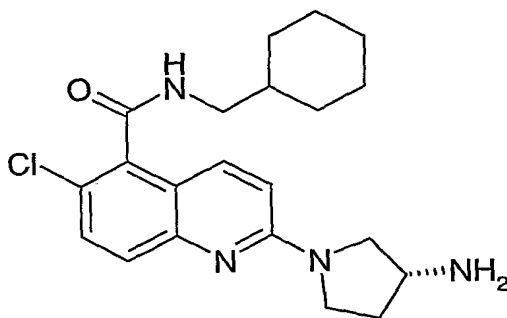
^1H NMR (400 MHz, d_6 -DMSO) δ 8.72 (1H, t), 8.00 (1H, d), 7.97 (1H, d), 7.76 (1H, d), 7.56 (1H, d), 3.46 (2H, t), 3.22-3.18 (2H, m), 2.97 (2H, t), 2.68-2.62 (4H, m), 1.93 (2H, quin), 1.83-1.67 (4H, m), 1.66-1.53 (4H, m), 1.29-0.93 (5H, m).

MS: APCI(+ve) 418/420 ($\text{M}+\text{H}^+$).

5

Example 48

2-[(3R)-3-Amino-1-pyrrolidinyl]-6-chloro-N-(cyclohexylmethyl)-5-quinolinecarboxamide, dihydrochloride

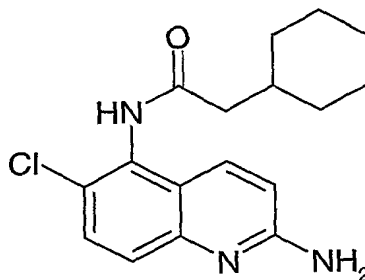


- 10 A stirred suspension of 2,6-dichloro-N-(cyclohexylmethyl)quinoline-5-carboxamide (Example 43(a)) (200 mg) and (3R)-3-pyrrolidinamine (0.20 mL) in acetonitrile (2 mL) was heated at 100°C in a microwave for 1 hour after which it was cooled to room temperature and concentrated. The residue was purified by chromatography (SiO_2 , dichloromethane: methanol: ammonia in methanol (7 M) (95:5:1), and then by HPLC
- 15 (Symmetry - 0.1% aqueous trifluoroacetic acid / acetonitrile). Conversion to the dihydrochloride salt by treatment with hydrochloric acid (4M in 1,4-dioxane) and subsequent recrystallisation (methanol / ethyl acetate) afforded the title compound as a solid (46 mg).
- 20 ^1H NMR (400 MHz, d_6 -DMSO, 90°C) δ 8.70-8.29 (3H, m), 8.04 (1H, d), 7.92 (1H, d), 7.67 (1H, d), 7.18 (1H, d), 4.07-3.87 (4H, m), 3.85-3.75 (1H, m), 3.24-3.18 (2H, m), 2.46-2.35 (1H, m), 2.33-2.23 (1H, m), 1.85-1.54 (6H, m), 1.33-0.95 (5H, m).
MS: APCI(+ve) 387/389 ($\text{M}+\text{H}^+$).

25 **Example 49**

N-(2-Amino-6-chloro-5-quinolinyl)-cyclohexaneacetamide, trifluoroacetate

113



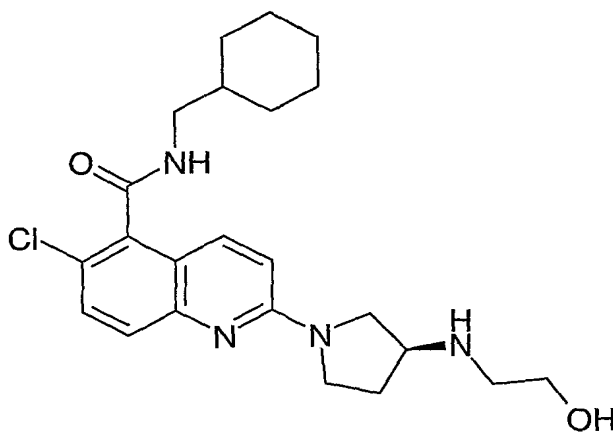
A stirred suspension of *N*-(2,6-dichloro-5-quinolinyl)-cyclohexanecarboxamide (Example 1 (a)) (200 mg) and *tetrabutylammonium* bromide (20 mg) in ammonium hydroxide (28% NH₃ in water) (1.0 mL) was heated at 180°C in a microwave for 3 hours after which it was cooled to room temperature and concentrated. Purification by HPLC (Symmetry - 0.1% aqueous trifluoroacetic acid / acetonitrile) gave the title compound as a solid (44 mg).

¹H NMR (400 MHz, d₆-DMSO) δ 10.03 (2H, s), 8.60 (1H, br), 8.10 (1H, d), 7.86 (1H, d), 7.59 (1H, d), 7.10 (1H, d), 2.35 (2H, d), 1.88-1.57 (6H, m), 1.31-0.97 (5H, m).

MS: APCI(+ve) 318/320 (M+H⁺).

Example 50

6-Chloro-*N*-(cyclohexylmethyl)-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-pyrrolidinyl]-5-quinolinecarboxamide, hydrochloride



a) 6-Chloro-*N*-(cyclohexylmethyl)-2-[(3*S*)-3-[[2-[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]amino]-1-pyrrolidinyl]-5-quinolinecarboxamide

A suspension of 2-[(3*S*)-3-amino-1-pyrrolidinyl]-6-chloro-*N*-(cyclohexylmethyl)-5-quinolinecarboxamide (Example 44) (0.16 g) and activated 3Å molecular sieves (0.16g) in anhydrous, degassed dichloromethane (7 mL) was treated with (*tert*-butyldimethylsilyloxy)acetaldehyde (0.078 mL) and the resulting mixture stirred at room temperature for 6 hours. To this mixture was added sodium triacetoxyborohydride (0.17g) and stirring continued for 16 hours. The reaction mixture was filtered and concentrated to dryness. Purification (SiO₂, Ethyl acetate:isohexane 4:1 as eluant) gave the sub-titled compound (0.17g).

¹H NMR (300 MHz, d₆-DMSO, 120°C) δ 8.05 (1H, s), 7.76 (1H, d), 7.51 (1H, d), 7.42 (1H, d), 6.89 (1H, d), 3.66 (2H, t), 3.76-3.42 (3H, m), 3.33-3.27 (1H, m), 3.21 (2H, t), 2.72 (2H, t), 2.19-2.08 (1H, m), 1.91-1.58 (8H, m), 1.33-0.98 (5H, m), 0.88 (9H, s), 0.05 (6H, s).

b) 6-Chloro-*N*-(cyclohexylmethyl)-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-pyrrolidinyl]-5-quinolinecarboxamide, hydrochloride

A mixture of 6-Chloro-*N*-(cyclohexylmethyl)-2-[(3*S*)-3-[[2-[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]amino]-1-pyrrolidinyl]-5-quinolinecarboxamide (Example 50(a)) (0.16 g) in 1,4-dioxane (1 mL) was treated with 4M HCl in 1,4-dioxane (1 mL) and stirred at room temperature for 16 hours. The reaction mixture was concentrated to dryness. Purification (HPLC, Symmetry - 0.1% aqueous trifluoroacetic acid / acetonitrile) followed by conversion of the resultant product to its hydrochloride salt by treatment with hydrochloric acid (4M in 1,4-dioxane) afforded the title product (0.05 g).

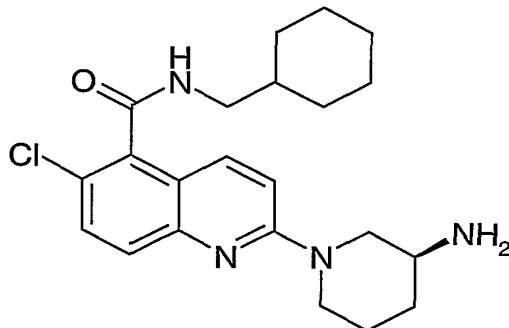
¹H NMR (300 MHz, d₆-DMSO, 120°C) δ 7.76 (1H, d), 7.52 (1H, d), 7.43 (1H, d), 6.90 (1H, d), 3.77-3.28 (6H, m), 3.20 (2H, d), 2.72-2.66 (2H, m), 2.20-2.08 (1H, m), 1.89-1.56 (8H, m), 1.32-0.96 (5H, m).

MS: APCI(+ve) 431/433 (M+H⁺).

m.p. 211-220°C

Example 51

2-[(3S)-3-Amino-1-piperidiny]-6-chloro-N-(cyclohexylmethyl)-5-quinolinecarboxamide



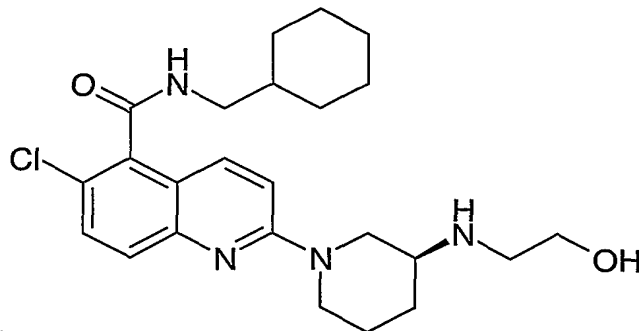
- 5 A stirred suspension of 2,6-dichloro-N-(cyclohexylmethyl)quinoline-5-carboxamide (Example 43(a)) (250 mg), (3S)-3-piperidinamine dihydrochloride (260 mg) and *tetrabutylammonium* bromide (20 mg) in acetonitrile (2 mL) was heated at 130°C in a microwave for 90 minutes after which it was cooled to room temperature and concentrated. The residue was purified by chromatography (SiO₂, dichloromethane: methanol: ammonia
10 in methanol (7 M) 96:3:1 as eluant) and subsequent recrystallisation (acetonitrile) gave the title compound as a solid (120 mg).

¹H NMR (400 MHz, d₆-DMSO) δ 8.64 (1H, t), 8.19 (2H, br s), 7.80 (1H, d), 7.57 (2H, s), 7.37 (1H, d), 4.55-4.47 (1H, m), 4.12-4.05 (1H, m), 3.30-3.14 (5H, m), 2.09-2.00 (1H, m),
15 1.89-1.49 (9H, m), 1.29-1.11 (3H, m), 1.04-0.91 (2H, m).
MS: APCI(+ve) 401/403 (M+H⁺).

Example 52

6-Chloro-N-(cyclohexylmethyl)-2-[(3S)-3-[(2-hydroxyethyl)amino]-1-piperidiny]-5-quinolinecarboxamide, hydrochloride
20

116



a) 6-Chloro-*N*-(cyclohexylmethyl)-2-[(3*S*)-3-[[2-[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]amino]-1-piperidinyl]-5-quinolinecarboxamide

Prepared according to the method of example 50(a) using 2-[(3*S*)-3-amino-1-piperidinyl]-6-chloro-*N*-(cyclohexylmethyl)-5-quinolinecarboxamide (Example 51) (200 mg), activated 3Å molecular sieves (0.20g), (*tert*-butyldimethylsilyloxy)acetaldehyde (0.085 mL), dichloromethane (5.0 mL) and sodium triacetoxyborohydride (210 mg). Purification (SiO₂, ethyl acetate:isohexane 1:1) gave the sub-titled compound (190 mg).

MS: APCI(+ve) 560/562 (M+H⁺).

b) 6-Chloro-*N*-(cyclohexylmethyl)-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-piperidinyl]-5-quinolinecarboxamide

Prepared according to the method of example 50(b) using 6-chloro-*N*-(cyclohexylmethyl)-2-[(3*S*)-3-[[2-[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]amino]-1-piperidinyl]-5-quinolinecarboxamide (Example 52(a)) (190 mg) and hydrochloric acid (4M in 1,4-dioxane) (2.0 mL). Purification (SiO₂, dichloromethane: methanol: ammonia in methanol (7 M) 96:3:1) and subsequent recrystallisation (acetonitrile) gave the title compound as a solid (53 mg).

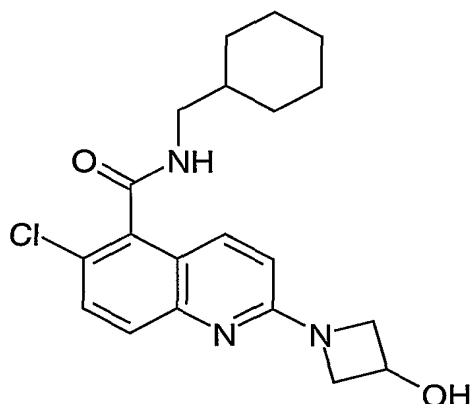
¹H NMR (400 MHz, d₆-DMSO) δ 8.61 (1H, t), 7.72 (1H, d), 7.52-7.50 (2H, m), 7.34 (1H, d), 4.50 (1H, t), 4.46-4.37 (1H, d), 4.30-4.22 (1H, d), 3.45 (2H, app q), 3.19-3.14 (2H, m),

3.13 - 3.04 (1H, m), 2.90-2.82 (1H, m), 2.73-2.65 (2H, m), 2.58-2.52 (1H, m), 1.95 (1H, m), 1.83-1.29 (9H, m), 1.28-1.09 (3H, m), 1.04-0.91 (2H, m).

MS: APCI(+ve) 445/447 (M+H⁺).

5 Example 53

6-Chloro-N-(cyclohexylmethyl)-2-(3-hydroxy-1-azetidiny)- 5-quinolinecarboxamide



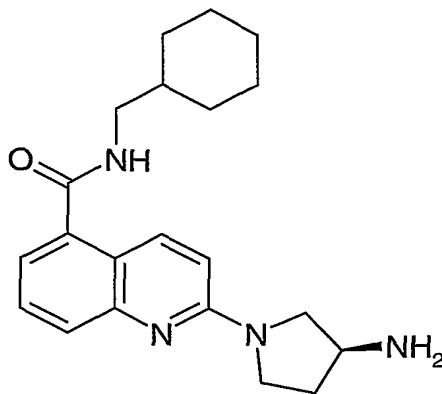
10 Prepared according to the method of example 30, using 2,6-dichloro-N-(cyclohexylmethyl)quinoline-5-carboxamide (Example 43(a)) (0.10 g), and hydroxy azetidine hydrochloride (0.30 g). Purification (HPLC, Symmetry - 0.1% aqueous trifluoroacetic acid / acetonitrile) afforded the title compound (0.04 g).

15 ¹H NMR (400 MHz, CD₃OD) δ 7.76 (1H, d), 7.56 (1H, d), 7.44 (1H, d), 6.70 (1H, d), 4.63 (1H, tt), 4.32 (2H, dd), 3.87 (2H, dd), 3.19 (2H, d), 1.82-1.49 (6H, m), 1.28-0.91 (5H, m).
MS: APCI(+ve) 374/376 (M+H⁺).
m.p. 206-208°C

20 Example 54

2-[(3S)-3-Amino-1-pyrrolidinyl]-N-(cyclohexylmethyl)-5-quinolinecarboxamide

118

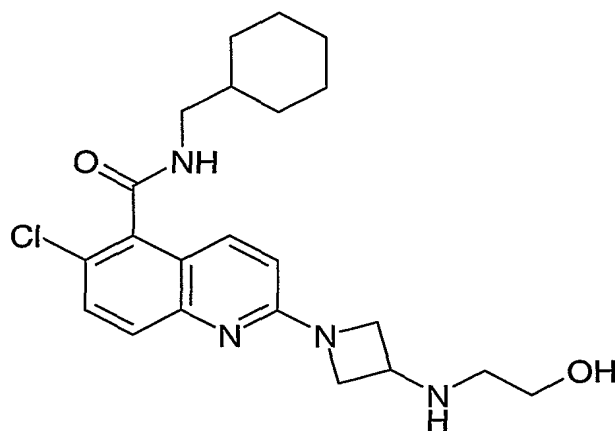


A suspension of 2-[(3*S*)-3-amino-1-pyrrolidinyl]-6-chloro-*N*-(cyclohexylmethyl)- 5-quinolinecarboxamide (Example 44) (0.10 g) and triethylamine (0.04 mL) in ethanol (20 mL) was treated with 5% palladium on charcoal (0.05 g) and stirred under 2 atmospheres of hydrogen at ambient temperature for 16 hours. The reaction mixture was filtered through Celite and the liquors concentrated to dryness. Recrystallisation from methanol/ethyl acetate afforded to title compound (0.05 g).

¹H NMR (300 MHz, CD₃OD) δ 8.28 (1H, dd), 7.78 (1H, d), 7.47 (1H, dt), 7.26 (1H, d), 6.89 (1H, dd), 4.02-3.94 (1H, m), 3.91-3.85 (1H, m), 3.77-3.61 (3H, m), 3.18 (2H, d), 2.50-2.37 (1H, m), 2.19-2.08 (1H, m), 1.82-1.49 (6H, m), 1.32-0.88 (5H, m).
MS: APCI(+ve) 353 (M+H⁺).
m.p. 127-128°C

Example 55

6-Chloro-*N*-(cyclohexylmethyl)-2-[3-[(2-hydroxyethyl)amino]-1-azetidiny]- 5-quinolinecarboxamide



a) 6-Chloro-*N*-(cyclohexylmethyl)-2-[3-[[2-[(methylsulfonyl)oxy]ethyl]amino]-1-azetidiny]-5-quinolinecarboxamide

- 5 Prepared according to the method of example 33(a), using 6-chloro-*N*-(cyclohexylmethyl)-2-(3-hydroxy-1-azetidiny)-5-quinolinecarboxamide (Example 53) (0.55 g) to afford the title compound (0.18 g).

MS: APCI(+ve) 453/455 (M+H⁺).

10

b) 6-Chloro-*N*-(cyclohexylmethyl)-2-[3-[(2-hydroxyethyl)amino]-1-azetidiny]-5-quinolinecarboxamide

Prepared according to the method of example 33(b), using 6-chloro-*N*-(cyclohexylmethyl)-2-[3-[[2-[(methylsulfonyl)oxy]ethyl]amino]-1-azetidiny]-5-quinolinecarboxamide

- 15 (Example 55(a)) (0.10 g) and ethanolamine (0.3 mL) to afford the title compound (0.03 g).

¹H NMR (300 MHz, CD₃OD) δ 7.76 (1H, d), 7.56 (1H, d), 7.44 (1H, d), 6.70 (1H, d), 4.29 (2H, t), 3.84 (2H, dd), 3.76 (1H, tt), 3.56 (2H, t), 3.22 (2H, d), 2.65 (2H, t), 1.83-1.48 (6H, m), 1.31-0.89 (5H, m).

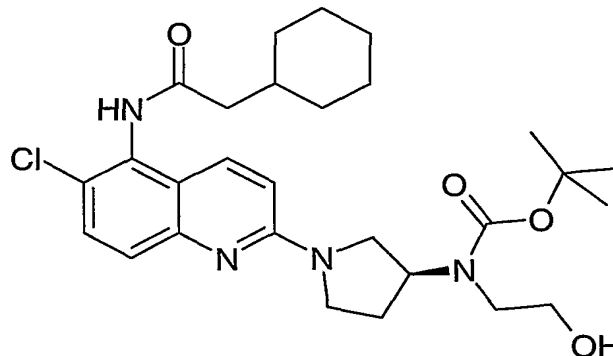
20

MS: APCI(+ve) 417/419 (M+H⁺).

m.p. 150-151°C

Example 56

[1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-3-pyrrolidinyl](2-hydroxyethyl)-carbamic acid 1,1-dimethylethyl ester



To a stirred solution of *N*-[6-chloro-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide (Example 36) (1 g) in dichloromethane (5 mL) and methanol (2 mL) was added di-*tert*-butyl-carbonate (1 g). The mixture was stirred at room temperature for 18 hours and absorbed onto silica. Purification (SiO₂, methanol:dichloromethane 5:95 as eluant) gave the title compound as a solid (400 mg).

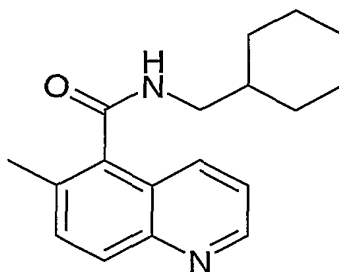
¹H NMR (300 MHz, d₆-DMSO/ CD₃OD, major rotamer) δ 7.84 (1H, d), 7.60 (1H, d), 7.53 (1H, d), 6.76 (1H, d), 4.68 (1H, m), 3.90-3.75 (2H, m), 3.74-3.63 (2H, m), 3.59-3.49 (4H, m), 3.42-3.27 (2H, m), 2.40 (2H, d), 2.31-2.18 (2H, m), 2.00-1.87 (2H, m), 1.71-1.65 (2H, m), 1.49 (9H, s), 1.40-1.01 (5H, m).

MS: APCI(+ve) 531.5/533.5 (M+H⁺).

m.p. 115-120°C.

Example 57

***N*-(Cyclohexylmethyl)-6-methyl-5-quinolinecarboxamide**



Prepared according to the method of example 42, using 5-bromo-6-methylquinoline (prepared according to the method of Khimiya Geterotsiklicheskikh Soedinenii 1988, 8,

1084) (4.0 g), cyclohexanemethylamine (4.2 mL), triethylamine (2.4 mL), dichlorobis(triphenylphosphine)palladium(II) (1.6 g) in *N*-methyl pyrrolidinone (40 mL) to afford the title compound (3.9 g)

- 5 ^1H NMR (300 MHz, $\text{d}_6\text{-DMSO}$) δ 8.86 (1H, dd), 8.58 (1H, t), 8.07 (1H, d), 7.95 (1H, d), 7.64 (1H, d), 7.54 (1H, dd), 3.21 (2H, t), 2.43 (3H, s), 1.83-1.52 (6H, m), 1.31-1.09 (3H, m), 1.05-0.91 (2H, m).

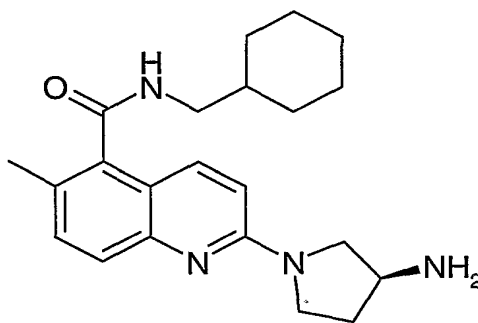
MS: APCI(+ve) 283.1 ($\text{M}+\text{H}^+$).

m.p. 165°C.

10

Example 58

2-[(3*S*)-3-Amino-1-pyrrolidinyl]-*N*-(cyclohexylmethyl)-6-methyl-5-quinolinecarboxamide, acetate



15

a) 2-Chloro-*N*-(cyclohexylmethyl)-6-methyl-5-quinolinecarboxamide

Prepared according to the method of example 43(a), using *N*-(cyclohexylmethyl)-6-methyl-5-quinolinecarboxamide (Example 57) (3 g), peracetic acid (3.3 g, 45% in acetic acid), glacial acetic acid (20 mL) and subsequently phosphorous oxychloride (20 mL) to afford the sub-titled compound (1.5 g).

20

MS: APCI(+ve) 317.3/319.1 ($\text{M}+\text{H}^+$).

b) 2-[(3*S*)-3-Amino-1-pyrrolidinyl]-*N*-(cyclohexylmethyl)-6-methyl-5-quinolinecarboxamide, acetate

25

Prepared according to the method of example 30, using 2-chloro-*N*-(cyclohexylmethyl)-6-methyl-5-quinolinecarboxamide (Example 58(a)) (0.450 g) and (3*S*)-3-pyrrolidinamine (0.500 g). Purification (HPLC, Symmetry - 0.1% aqueous ammonium acetate / acetonitrile) afforded the title compound (0.110 g).

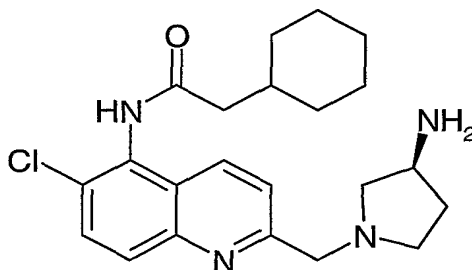
5

¹H NMR (400 MHz, d₆-DMSO) δ 8.43 (1H, t), 7.73 (1H, d), 7.45 (1H, d), 7.32 (1H, d), 6.84 (1H, d), 3.69-3.56 (3H, m), 3.51 (1H, m), 3.22 (1H, m), 3.16 (2H, t), 2.30 (3H, s), 2.08 (1H, m), 1.87 (3H, s), 1.81-1.66 (5H, m), 1.66-1.49 (2H, m), 1.30-1.08 (3H, m), 1.04-0.89 (2H, m).

10 MS: APCI(+ve) 367.3 (M+H⁺).
m.p. 154-155°C

Example 59

N-[2-[(3*S*)-3-Amino-1-pyrrolidinyl]methyl]-6-chloro-5-quinolinyl]-
15 cyclohexaneacetamide



a) *N*-(6-Chloro-2-ethenyl-5-quinolinyl)-cyclohexaneacetamide

To a solution of *N*-(2,6-dichloro-5-quinolinyl)-cyclohexaneacetamide (Example 1(a)) (2 g)
20 in dimethylformamide (6 mL) was added tributyl(vinyl)tin (3.63 g), 2,6-*di*-*tert*-butyl-4-methylphenol (50 mg) and dichlorobis(triphenylphosphine)palladium (0.25 g). The reaction was heated at 80°C under nitrogen for 6 hours and then cooled to room temperature. The mixture was filtered through diatomaceous earth and poured into water and dichloromethane. The organic layer was separated and the aqueous was further
25 extracted with dichloromethane. The combined organic layers were dried, filtered and evaporated. Purification (SiO₂, methanol:dichloromethane 5:95 as eluant) gave the sub-titled compound (1.2 g).

MS: APCI(+ve) 329.4/331.2 (M+H⁺).

b) ***N*-(6-Chloro-2-formyl-5-quinolinyl)-cyclohexaneacetamide**

- 5 Ozone was bubbled through a solution of *N*-(6-chloro-2-ethenyl-5-quinolinyl)-cyclohexaneacetamide (Example 59(a)) (1.2 g) in dichloromethane (40 mL) and acetic acid (1 mL) at -78°C for 2 hours. Dimethylsulfide (2 mL) was added and the solution allowed to warm to room temperature overnight. Saturated aqueous sodium bicarbonate was added and the mixture stirred rapidly. The aqueous phase was separated and further extracted
10 with dichloromethane. The combined organic extracts were dried, filtered and evaporated to yield the sub-titled compound (0.7 g).

MS: APCI(+ve) 331/333 (M+H⁺).

- 15 c) ***N*-[2-[[*(3S)*-3-Amino-1-pyrrolidinyl]methyl]-6-chloro-5-quinolinyl]-cyclohexaneacetamide**

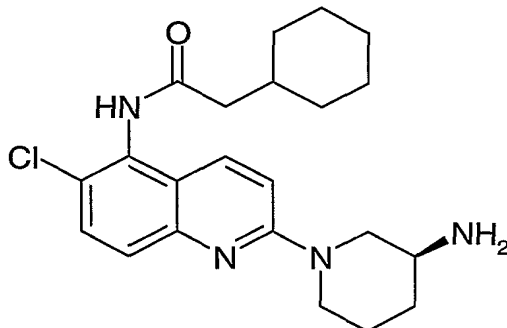
To a solution of *N*-(6-chloro-2-formyl-5-quinolinyl)-cyclohexaneacetamide (Example 59 (b)) (0.68 g) in dichloromethane (10 mL) and methanol (1 mL) was added (*(3S)*-3-pyrrolidinyl-carbamic acid, 1,1-dimethylethyl ester (1.1 g). The mixture was stirred for 2
20 hours and then sodium triacetoxyborohydride (1.2 g) added. The mixture was stirred overnight and then poured into water. The product was filtered off and suspended in methanol (2 mL). Treatment with hydrochloric acid (4M in 1,4-dioxane) yielded the crude product which was purified by HPLC (Symmetry - 0.1% aqueous ammonium acetate / acetonitrile) to afford the titled product (29 mg).

25

¹H NMR (400 MHz, d₆-DMSO) δ 11.31 (1H, s), 10.14 (1H, s), 8.64 (3H, s), 8.33 (1H), 8.04 (1H, d), 7.96 (1H, d), 7.78 (1H, d), 4.9 (2H, s), 4.12-3.50 (5H, m), 2.40 (2H, d), 2.19 (1H, m), 1.93-1.58 (7H, m), 1.35-1.00 (5H, m).

MS: APCI(+ve) 401.2/403.2 (M+H⁺).

- 30 m.p. 160°C dec

Example 60***N*-[2-[(3*S*)-3-Amino-1-piperidinyl]-6-chloro-5-quinoliny]-cyclohexaneacetamide**

5 *N*-(2,6-Dichloro-5-quinoliny)-cyclohexaneacetamide (Example 1(a)) (0.2 g), (3*S*)-3-piperidinamine (0.089 g) and triethylamine (0.25 mL) were placed into a 10 mL microwave vial followed by the addition of acetonitrile (5mL). The vial was sealed and heated at 120°C in a single mode microwave for 30 minutes, and a further 60 minutes at 150°C. The product crystallised from the reaction on cooling and was subsequently filtered
10 and washed with acetonitrile (10 mL). Purification (SiO₂, 7M ammonia in methanol:methanol:dichloromethane 1:4:95) gave the title compound (0.055 g).

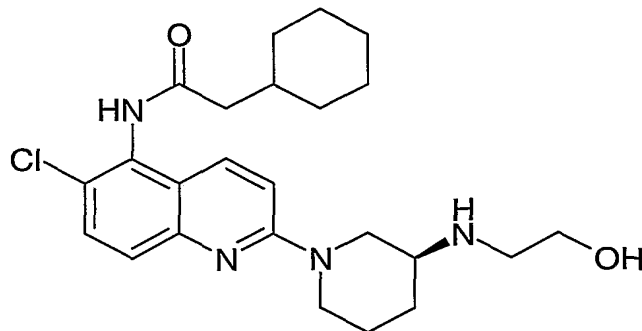
¹H NMR (400 MHz, CD₃OD) δ 7.91 (1H, d), 7.56 (2H, s), 7.22 (1H, d), 4.47-4.42 (1H, m), 4.33-4.25 (1H, m), 3.14-3.06 (1H, m), 2.92-2.78 (2H, m), 2.41 (2H, d), 2.07-1.99 (1H, m),
15 1.98-1.88 (3H, m), 1.87-1.75 (3H, m), 1.75-1.67 (1H, m), 1.66-1.53 (1H, m), 1.47-1.21 (4H, m), 1.19-1.08 (2H, m).

MS: APCI(+ve) 401.2 (M+H⁺).

m.p. 173-176 °C

20 Example 61***N*-[6-Chloro-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-piperidinyl]-5-quinoliny]-cyclohexaneacetamide**

125



a) ***N*-[6-Chloro-2-[(3*S*)-3-[[2-[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]amino]-1-piperidinyl]-5-quinoliny]-cyclohexaneacetamide**

5 Prepared according to the method of example 50(a), using *N*-[2-[(3*S*)-3-amino-1-piperidinyl]-6-chloro-5-quinoliny]-cyclohexaneacetamide (Example 60) (200 mg), (*tert*-butyldimethylsilyloxy)acetaldehyde (0.086 mL) and sodium triacetoxyborohydride (0.212 g) to afford the sub-title compound (0.2 g).

10 MS: APCI(+ve) 559.5/561.5 (M+H⁺).

b) ***N*-[6-Chloro-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-piperidinyl]-5-quinoliny]-cyclohexaneacetamide**

15 Prepared according to the method of example 50(b), using *N*-[6-chloro-2-[(3*S*)-3-[[2-[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]amino]-1-piperidinyl]-5-quinoliny]-cyclohexaneacetamide (Example 61(a)) (200 mg) and 4M hydrogen chloride in 1,4-dioxane (2 mL). Purification (SiO₂, methanol:dichloromethane 5:95 as eluant) gave the title compound as a solid (56 mg).

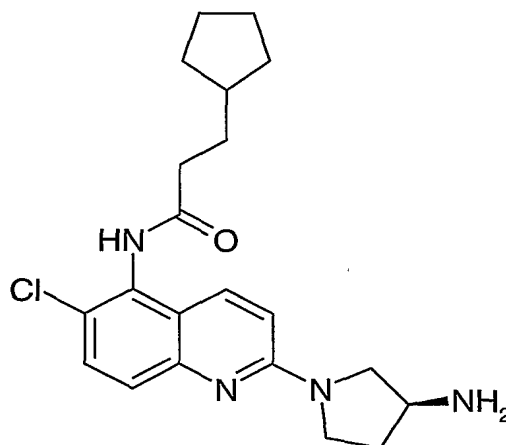
20 ¹H NMR (400 MHz, CD₃OD) δ 7.96 (1H, d), 7.60 (2H, s), 7.27 (1H, d), 4.54 (1H, d), 4.02 (1H, d), 3.77 (2H, t), 3.58-3.49 (1H, m), 3.42-3.31 (2H, m), 3.24-3.16 (3H, m), 2.34 (2H, d), 2.23-2.14 (1H, m), 1.93-1.57 (8H, m), 1.33-0.98 (5H, m).

MS: APCI(+ve) 445.2/447.1 (M+H⁺).

m.p. 182-183°C

25

Example 62

***N*-[2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-chloro-5-quinolinyl]-cyclopentanepropanamide****a) *N*-(2,6-Dichloro-5-quinolinyl)-cyclopentanepropanamide**

- 5 To a stirred solution of cyclopentanepropanoic acid (1 g) in dichloromethane (5 mL) at 0°C under nitrogen, was added *N,N*-dimethylformamide (1 drop) and oxalyl chloride (2 mL). The reaction mixture was stirred at room temperature for 2 hours, then evaporated to dryness and redissolved in dichloromethane (2 mL). The solution was added to a mixture of 2,6-dichloroquinolin-5-amine (Example 1(d)) (500 mg) and potassium carbonate (650
- 10 mg) in acetone (10 mL). The reaction mixture was stirred at room temperature for 16 hours. The resulting solid was collected by filtration and subsequently washed with water (10 mL) to afford the sub-title compound (530 mg).

¹H NMR (400 MHz, d₆-DMSO) δ 8.27 (1H, d), 7.96-7.85 (2H, m), 7.66 (1H, d), 2.57-2.40 (2H, m), 1.93-1.44 (9H, m), 1.21-1.07 (2H, m).

MS: APCI(+ve) 337.2/339.2 (M+H⁺).

b) *N*-[2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-chloro-5-quinolinyl]-cyclopentanepropanamide

- 20 Prepared according to the method of example 30, using *N*-(2,6-dichloro-5-quinolinyl)-cyclopentanepropanamide (Example 62(a)) (500 mg) and (3*S*)-3-pyrrolidinamine (390 mg). Purification (SiO₂, methanol:dichloromethane:ammonium hydroxide solution 7:93:1 as eluant) gave the title compound as a solid (400 mg).

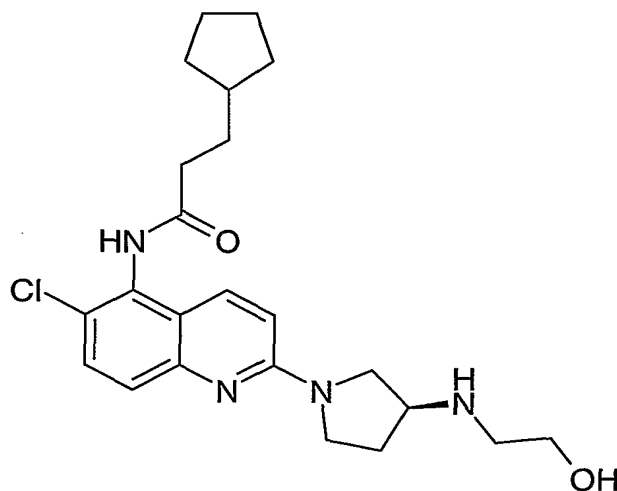
^1H NMR (400 MHz, d_6 -DMSO) δ 9.76 (1H, s), 7.83 (1H, d), 7.54 (1H, d), 7.46 (1H, d), 6.90 (1H, d), 3.74-3.45 (4H, m), 3.39-3.15 (1H, m), 2.44 (2H, t), 2.07 (1H, td), 1.92-1.45 (12H, m), 1.22-1.07 (2H, m).

MS: APCI(+ve) 387.1/389.1 ($\text{M}+\text{H}^+$).

5 m.p. 192-194°C.

Example 63

N-[6-Chloro-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-pyrrolidinyl]-5-quinolinyl]-
10 cyclopentanepropanamide



15 a) *N*-[6-Chloro-2-[(3*S*)-3-[[2-[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]amino]-1-pyrrolidinyl]-5-quinolinyl]-cyclopentanepropanamide

Prepared according to the method of example 50(a), using *N*-[2-[(3*S*)-3-amino-1-pyrrolidinyl]-6-chloro-5-quinolinyl]-cyclopentanepropanamide (Example 62) (300 mg) and [[(1,1-dimethylethyl)dimethylsilyl]oxy]-acetaldehyde (133 μl). Purification (SiO_2 , methanol:dichloromethane 3:97 as eluant) gave the sub-title compound as a solid (200
20 mg).

¹H NMR (400 MHz, d₆-DMSO) δ 9.80 (1H, s), 7.88 (1H, d), 7.58 (1H, d), 7.50 (1H, d), 6.96 (1H, d), 3.85-3.16 (9H, m), 2.77-2.68 (2H, m), 2.48 (2H, t), 2.22-2.10 (1H, m), 1.95-1.48 (9H, m), 1.24-1.12 (2H, m), 0.90 (9H, s), 0.08 (6H, s).

MS: APCI(+ve) 545.5/547.5 (M+H⁺).

5

b) *N*-[6-Chloro-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-pyrrolidinyl]-5-quinolinyl]-cyclopentanepropanamide

To a stirred solution of *N*-[6-chloro-2-[(3*S*)-3-[[2-[(1,1-

dimethylethyl)dimethylsilyl]oxy]ethyl]amino]-1-pyrrolidinyl]-5-quinolinyl]-

10 cyclopentanepropanamide (Example 63(a)) (200 mg) in dichloromethane:methanol 1:1 (3 mL) under nitrogen, was added HCl (1 mL, 4M solution in dioxane). The reaction mixture was stirred at room temperature for 30 minutes, then evaporated to dryness. Purification (HPLC, Symmetry - 0.1% aqueous trifluoroacetic acid / acetonitrile) gave the title compound as a solid (35 mg).

15

¹H NMR (400 MHz, d₆-DMSO) δ 9.77 (1H, s), 7.84 (1H, d), 7.54 (1H, d), 7.47 (1H, d), 6.92 (1H, d), 4.54 (1H, s), 3.75-3.40 (6H, m), 2.72-2.61 (2H, m), 2.44 (2H, t), 2.20-2.06 (1H, m), 1.92-1.74 (4H, m), 1.71-1.45 (6H, m), 1.22-1.06 (2H, m).

MS: APCI(+ve) 431.2/433.2 (M+H⁺).

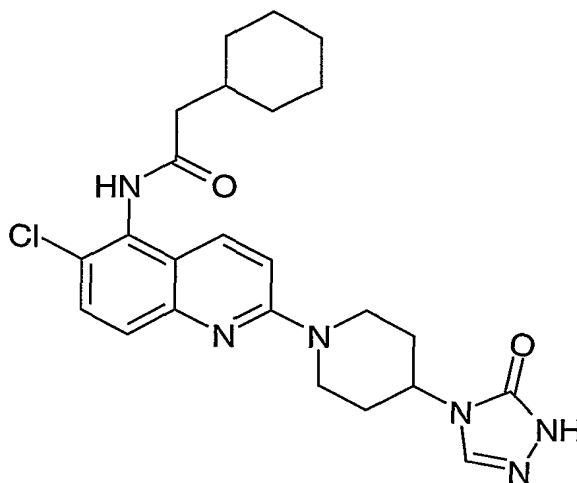
20 m.p. 186-188 °C

Example 64

***N*-[6-Chloro-2-[4-(1,5-dihydro-5-oxo-4*H*-1,2,4-triazol-4-yl)-1-piperidinyl]-5-quinolinyl]-cyclohexaneacetamide**

25

129



a) 2-Formyl-N-[1-(phenylmethyl)-4-piperidinyl]-hydrazinecarboxamide

1-(Phenylmethyl)-4-piperidinamine (3 g) in dichloromethane (10 mL) and triethylamine (4.5 mL) were added dropwise to a stirred solution of triphosgene (1.55 g) in dichloromethane (20 mL) at 0°C under nitrogen. The reaction mixture was allowed to warm to room temperature and stirred for 30 minutes. The mixture was cooled to 0°C and formyl hydrazine (1.4 g) and triethylamine (4.5 mL) were added. The reaction was stirred at room temperature for 1 hour and then evaporated to dryness. Purification (SiO₂, methanol:dichloromethane:ammonium hydroxide solution 5:95:1 as eluant) gave the sub-title compound (2.5 g).

MS: APCI(+ve) 277.2 (M+H⁺).

b) 2,4-Dihydro-4-[1-(phenylmethyl)-4-piperidinyl]-3H-1,2,4-triazol-3-one

2-Formyl-N-[1-(phenylmethyl)-4-piperidinyl]-hydrazinecarboxamide (Example 64(a)) (2.5 g) was divided between 5 x 10 mL vials. Potassium hydroxide (5 mL, 1 M solution in methanol) was added to each vial and the reactions were heated at 90°C for 35 minutes within a microwave. The combined products were acidified to pH6 with aqueous 2M hydrochloric acid and were then evaporated to dryness. Purification (SiO₂, methanol:dichloromethane:acetic acid 15:85:1 as eluant) gave the sub-title compound as an oil (2.2 g).

MS: APCI(+ve) 259.2 (M+H⁺).

c) 2,4-Dihydro-4-(4-piperidiny)-3H-1,2,4-triazol-3-one

2,4-Dihydro-4-[1-(phenylmethyl)-4-piperidiny]-3H-1,2,4-triazol-3-one (Example 64(b))
5 (2.2 g) was divided between 2, 10 mL vials. 1,4-Cyclohexadiene (5 mL) and palladium hydroxide (270 mg, 20 wt. % on carbon) were added to each vial and the reactions were heated at 100°C for 30 minutes within a microwave. The reaction mixtures were combined, ethanol (50 mL) and water (50 mL) were added and the mixture was filtered through diatomaceous earth and evaporated to give the sub-title compound as a solid (720 mg).

10 MS: APCI(+ve) 169.2 (M+H⁺).

d) N-[6-Chloro-2-[4-(1,5-dihydro-5-oxo-4H-1,2,4-triazol-4-yl)-1-piperidiny]-5-quinoliny]-cyclohexaneacetamide

15 Prepared according to the method of example 30, using N-(2,6-dichloro-5-quinoliny)-cyclohexaneacetamide (Example 1(a)) (150 mg) and 2,4-dihydro-4-(4-piperidiny)-3H-1,2,4-triazol-3-one (Example 64 (c)) (225 mg). Methanol (10 mL) and dichloromethane (10 mL) were added to the reaction mixture and the solid was collected by filtration to afford the title compound (40 mg).

20 ¹H NMR (400 MHz, d₆-DMSO) 11.64 (1H, s), 9.80 (1H, s), 7.99 (1H, s), 7.87 (1H, d), 7.59 (1H, d), 7.50 (1H, d), 7.39 (1H, d), 4.71 (2H, d), 4.13-4.01 (1H, m), 3.05 (2H, t), 2.33 (2H, d), 1.99-1.59 (10H, m), 1.34-0.98 (5H, m).

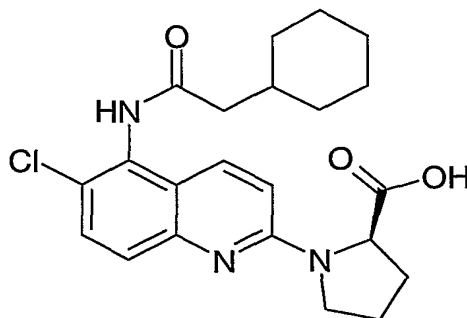
MS: APCI(+ve) 469.1/471.1 (M+H⁺).

25 m.p. 310-313 °C

Example 65

1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinoliny]-D-proline, trifluoroacetate

131



a) 1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-D-proline, 1,1-dimethylethyl ester

Prepared according to the method of example 30, using *N*-(2,6-dichloro-5-quinolinyl)-cyclohexaneacetamide (Example 1 (a)) (200 mg) and 1,1-dimethylethyl ester D-proline (308 mg). Purification (SiO₂, ethyl acetate:*isohexane* 25:75 as eluant) gave the sub-title compound as an oily solid (200 mg).

MS: APCI(+ve) 472.5/474.5 (M+H⁺).

b) 1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-D-proline, trifluoroacetate

Trifluoroacetic acid (1 mL) was added to a stirred solution of 1-[6-chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-D-proline 1,1-dimethylethyl ester (Example 65(a)) (200 mg) in dichloromethane (3 mL). The reaction was stirred at room temperature for 3 hours and then evaporated to dryness. Purification (SiO₂, methanol:dichloromethane 10:90 as eluant) gave the title compound as a solid (150 mg).

¹H NMR (400 MHz, d₆-DMSO) 9.58 (1H, s), 7.97 (1H, d), 7.67 - 7.56 (2H, m), 7.02 (1H, d), 4.74 (1H, dd), 3.78 - 3.62 (2H, m), 2.42 - 2.26 (3H, m), 2.22 - 1.96 (3H, m), 1.93 - 1.57 (6H, m), 1.36 - 1.01 (5H, m).

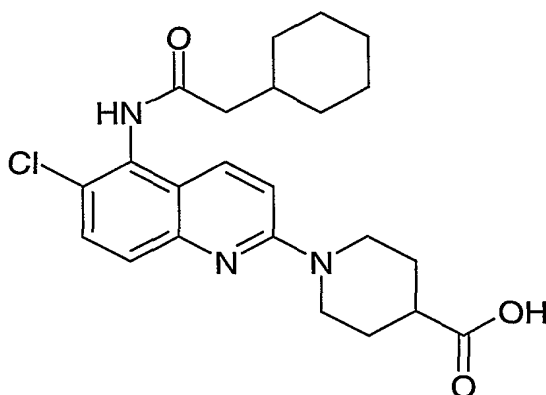
MS: APCI(+ve) 416.1/418.1 (M+H⁺).

m.p. 170-173 °C

Example 66

1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-4-piperidinecarboxylic acid, lithium salt

132



a) 1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-4-piperidinecarboxylic acid, ethyl ester

5 Prepared according to the method of example 30, using *N*-(2,6-dichloro-5-quinolinyl)-cyclohexaneacetamide (Example 1(a)) (200 mg) and 4-piperidinecarboxylic acid, ethyl ester (280 mg). Purification (SiO₂, ethyl acetate:*iso*hexane 25:75 as eluant) gave the sub-title compound as an oil (200 mg).

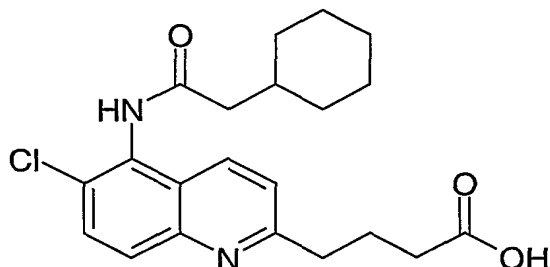
10 MS: APCI(+ve) 458.5/460.5 (M+H⁺).

b) 1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-4-piperidinecarboxylic acid, lithium salt

15 To a stirred suspension of 1-[6-chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-4-piperidinecarboxylic acid ethyl ester (Example 66(a)) (200 mg) in methanol (2 mL) was added lithium hydroxide (30 mg) in water (2 mL). The mixture was stirred at 50°C for 6 hours and then allowed to cool to room temperature. The solid was collected by filtration and subsequently washed with water (10 mL) to afford the titled compound (40 mg).

20 ¹H NMR (400 MHz, d₆-DMSO) δ 9.78 (1H, s), 7.85 (1H, d), 7.57 (1H, d), 7.48 (1H, d), 7.32 (1H, d), 4.41 (2H, d), 3.08 (2H, t), 2.58-2.45 (1H, m), 2.32 (2H, d), 1.97-1.46 (10H, m), 1.35-0.95 (5H, m).

MS: APCI(+ve) 430.2/432.2 (M+H⁺).

Example 67**6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinebutanoic acid**

5

a) *N*-[6-chloro-2-(3-cyanopropyl)-5-quinolinyl]-cyclohexaneacetamide

Bromo(3-cyanopropyl)-zinc (30 mL, 0.5 M in tetrahydrofuran) and tetrakis(triphenylphosphine)palladium(0) (86 mg) were added to *N*-(2,6-dichloro-5-quinolinyl)-cyclohexaneacetamide (Example 1(a)) (500 mg). The reaction mixture was heated to reflux for 30 minutes. The mixture was cooled to room temperature and then poured into aqueous saturated ammonium chloride solution (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried, filtered and evaporated. Purification (SiO₂, methanol:dichloromethane 3:97 as eluant) gave the sub-

10 title compound as a solid (490 mg).

15

¹H NMR (500 MHz, d₆-DMSO) δ 9.96 (1H, s), 8.13 (1H, d), 7.92 (1H, d), 7.82 (1H, d), 7.56 (1H, d), 3.04 (2H, t), 2.61 (2H, t), 2.37 (2H, d), 2.09 (2H, quintet), 1.90-1.78 (2H, m), 1.76-1.60 (4H, m), 1.33-1.12 (3H, m), 1.11-1.01 (2H, m).

MS: APCI(+ve) 370.4/372.4 (M+H⁺).

20

b) 6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinebutanoic acid

Potassium hydroxide (2 mL, 50 % solution in water) was added to a stirred solution of *N*-[6-chloro-2-(3-cyanopropyl)-5-quinolinyl]-cyclohexaneacetamide (Example 67(a)) (190 mg) in methanol (2 mL). The reaction mixture was heated to 50°C for 6 hours then allowed

25 to cool. The mixture was acidified with aqueous 2M hydrochloric acid until a precipitate formed which was collected by filtration. Purification by HPLC (Symmetry - 0.1% aqueous ammonium acetate / acetonitrile) afforded the title compound as a solid (45 mg).

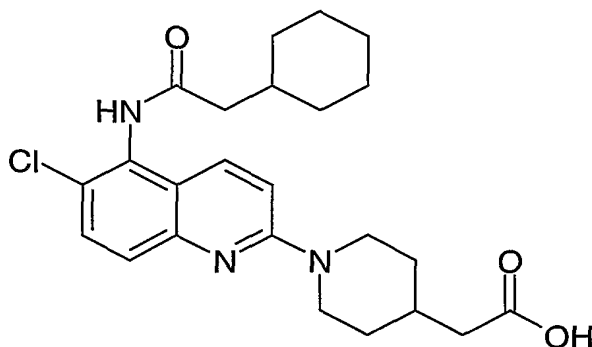
¹H NMR (400 MHz, d₆-DMSO) δ 9.99 (1H, s), 8.11 (1H, d), 7.90 (1H, d), 7.80 (1H, d), 7.51 (1H, d), 2.92 (2H, t), 2.36 (2H, d), 2.20 (2H, t), 1.96 (2H, quintet), 1.90-1.58 (6H, m), 1.34 0.98 (5H, m).

5 MS: APCI(+ve) 389.1/391.1 (M+H⁺).
m.p. 216-220 °C

Example 68

1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-4-piperidineacetic acid

10



a) 1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-4-piperidineacetic acid, ethyl ester

15 Prepared according to the method of example 30, using *N*-(2,6-dichloro-5-quinolinyl)-cyclohexaneacetamide (prepared as in Example 1(a)) (200 mg) and 4-piperidineacetic acid, ethyl ester (305 mg). The reaction mixture was evaporated to dryness, the residue was suspended in methanol and the solid collected by filtration to afford the sub-title compound (150 mg).

20

¹H NMR (400 MHz, d₆-DMSO) δ 9.77 (1H, s), 7.83 (1H, d), 7.56 (1H, d), 7.47 (1H, d), 7.31 (1H, d), 4.52 (2H, d), 4.07 (2H, q), 2.94 (2H, t), 2.36-2.19 (4H, m), 2.07-1.94 (1H, m), 1.89-1.58 (8H, m), 1.37-0.97 (10H, m).
MS: APCI(+ve) 472.5/474.5 (M+H⁺).

25

b) 1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-4-piperidineacetic acid

Prepared according to the method of Example 66(b), using 1-[6-chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-4-piperidineacetic acid, ethyl ester (Example 68(a)) (150 mg). Purification by HPLC (Symmetry - 0.1% aqueous ammonium acetate / acetonitrile) afforded the title compound as a solid (15 mg).

5

^1H NMR (400 MHz, d_6 -DMSO) δ 9.78 (1H, s), 7.83 (1H, d), 7.56 (1H, d), 7.47 (1H, d), 7.30 (1H, d), 4.52 (2H, d), 2.93 (2H, t), 2.32 (2H, d), 2.14 (2H, d), 2.04-1.58 (9H, m), 1.35-0.95 (7H, m).

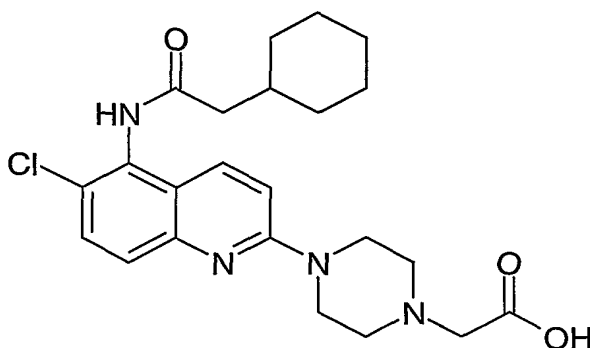
MS: APCI(+ve) 444.1/446.1 ($\text{M}+\text{H}^+$).

10 m.p. 242-244°C

Example 69

4-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-1-piperazineacetic acid, lithium salt

15



a) 4-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-1-piperazineacetic acid, ethyl ester

Prepared according to the method of example 30, using *N*-(2,6-dichloro-5-quinolinyl)-cyclohexaneacetamide (Example 1 (a)) (200 mg) and 1-piperazineacetic acid, ethyl ester (310 mg) to afford the sub-title compound as a solid (180 mg).

20

^1H NMR (400 MHz, d_6 -DMSO) δ 9.48 (1H, s), 7.88 (1H, d), 7.55 (1H, d), 7.48 (1H, d), 7.24 (1H, d), 4.11 (2H, q), 3.71 (4H, t), 3.27 (2H, s), 2.65 (4H, t), 2.37-2.26 (2H, m), 1.94-1.57 (6H, m), 1.35-0.97 (8H, m).

25

MS: APCI(+ve) 473.5/475.5 ($\text{M}+\text{H}^+$).

b) 4-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-1-piperazineacetic acid, lithium salt

Prepared according to the method of Example 66(b), using 4-[6-chloro-5-
5 [(cyclohexylacetyl)amino]-2-quinolinyl]-1-piperazineacetic acid ethyl ester
(Example 69(a)) (180 mg) to afford the title compound as a solid (80 mg).

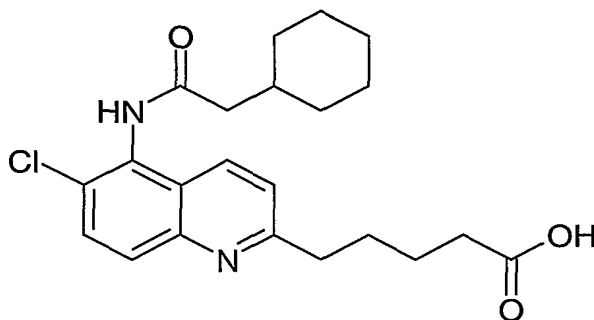
¹H NMR (400 MHz, d₆-DMSO) δ 8.02 (1H, d), 7.28 (1H, d), 6.97 (1H, d), 6.91 (1H, d),
3.61 (4H, s), 2.75 (2H, s), 2.51 (4H, s), 1.99 (2H, d), 1.91-1.55 (6H, m), 1.30-1.05 (3H, m),
10 0.99-0.85 (2H, m).

MS: APCI(+ve) 445.1/447.1 (M+H⁺).

m.p. 320-326 °C

Example 70

15 **6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinepentanoic acid**



a) N-[6-Chloro-2-(4-cyanobutyl)-5-quinolinyl]-cyclohexaneacetamide

Prepared according to the method of example 67(a), using N-(2,6-dichloro-5-quinolinyl)-
20 cyclohexaneacetamide (Example 1 (a)) (500 mg) and bromo(4-cyanobutyl)-zinc (30 mL,
0.5 M solution in tetrahydrofuran). Purification (SiO₂, methanol:dichloromethane 1:99 as
eluant) gave the sub-title compound (600 mg).

¹H NMR (400 MHz, d₆-DMSO) δ 9.95 (1H, s), 8.12 (1H, d), 7.91 (1H, d), 7.81 (1H, d),
25 7.54 (1H, d), 2.96 (2H, t), 2.56 (2H, t), 2.36 (2H, d), 1.91-1.54 (10H, m), 1.34-0.98 (5H,
m).

MS: APCI(+ve) 384.5/386.5 ($M+H^+$).

b) 6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinepentanoic acid

Prepared according to the method of example 67(b), using *N*-[6-chloro-2-(4-cyanobutyl)-5-quinolinyl]-cyclohexaneacetamide (Example 70(a)) (200 mg). Purification by HPLC (Symmetry - 0.1% aqueous ammonium acetate / acetonitrile) afforded the title compound as a solid (25 mg).

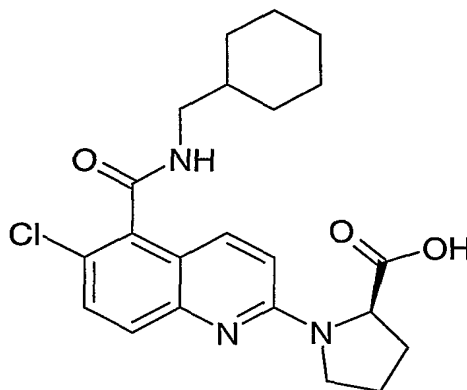
1H NMR (400 MHz, d_6 -DMSO) δ 9.96 (1H, s), 8.11 (1H, d), 7.90 (1H, d), 7.80 (1H, d), 7.52 (1H, d), 2.92 (2H, t), 2.36 (2H, d), 2.23 (2H, t), 1.93-1.50 (10H, m), 1.34-0.98 (5H, m).

MS: APCI(-ve) 401.2/403.2 ($M-H^+$).

m.p. 199-201 °C

Example 71

1-[6-Chloro-5-[[[(cyclohexylmethyl)amino]carbonyl]-2-quinolinyl]-D-proline



a) 1-[6-Chloro-5-[[[(cyclohexylmethyl)amino]carbonyl]-2-quinolinyl]-D-proline 1,1-dimethylethyl ester

Prepared according to the method of example 30, using 2,6-dichloro-*N*-(cyclohexylmethyl)-5-quinolinecarboxamide (Example 43(a)) (200 mg) and *D*-proline, 1,1-dimethylethyl ester (310 mg). Purification (SiO₂, ethyl acetate:*isohexane* 30:70 as eluant) gave the sub-title compound as an oil (250 mg).

MS: APCI(+ve) 472.5/474.5 ($M+H^+$).

b) 1-[6-Chloro-5-[[[(cyclohexylmethyl)amino]carbonyl]-2-quinolinyl]-D-proline

Prepared according to the method of example 65(b), using 1-[6-chloro-5-

- 5 [[[(cyclohexylmethyl)amino]carbonyl]-2-quinolinyl]-D-proline 1,1-dimethylethyl ester (Example 71(a)) (250 mg). Purification (SiO_2 , methanol:dichloromethane 5:95 as eluant) gave the title compound as a solid (144 mg).

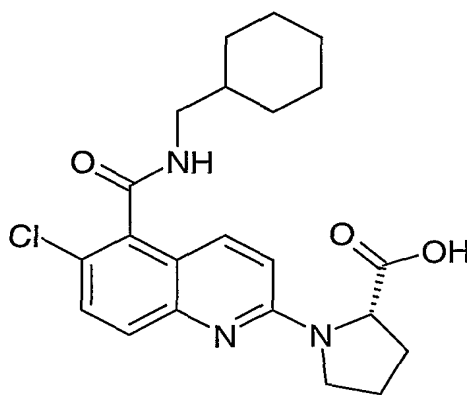
- 1H NMR (300 MHz, d_6 -DMSO) δ 8.66 (1H, t), 7.80 (1H, d), 7.56 (2H, s), 7.05 (1H, d),
10 4.67 (1H, d), 3.83-3.50 (2H, m), 3.17 (2H, t), 2.40-2.23 (1H, m), 2.18-1.90 (3H, m), 1.85-1.46 (6H, m), 1.34-0.86 (5H, m).

MS: APCI(+ve) 416.1/418.1 ($M+H^+$).

m.p. 157-160 °C

15 **Example 72**

1-[6-Chloro-5-[[[(cyclohexylmethyl)amino]carbonyl]-2-quinolinyl]-L-proline, trifluoroacetate



20

a) 1-[6-Chloro-5-[[[(cyclohexylmethyl)amino]carbonyl]-2-quinolinyl]-L-proline 1,1-dimethylethyl ester

Prepared according to the method of example 30, using 2,6-dichloro-N-

(cyclohexylmethyl)-5-quinolinecarboxamide (Example 43(a)) (200 mg) and L-proline, 1,1-

dimethylethyl ester (305 mg). Purification (SiO₂, ethyl acetate:*iso*hexane 20:80 as eluant) gave the sub-title compound as an oil (200 mg).

MS: APCI(+ve) 472.5/474.5 (M+H⁺).

5

b) 1-[6-Chloro-5-[[[(cyclohexylmethyl)amino]carbonyl]-2-quinoliny]]-L-proline, trifluoroacetate

Prepared according to the method of example 65(b), using 1-[6-chloro-5-

[[[(cyclohexylmethyl)amino]carbonyl]-2-quinoliny]]-L-proline 1,1-dimethylethyl ester

10 (Example 72(a)) (200 mg). Purification (SiO₂, methanol:dichloromethane 5:95 as eluant followed by HPLC - Symmetry - 0.1% aqueous trifluoroacetic acid / acetonitrile) gave the title compound as a solid (85 mg).

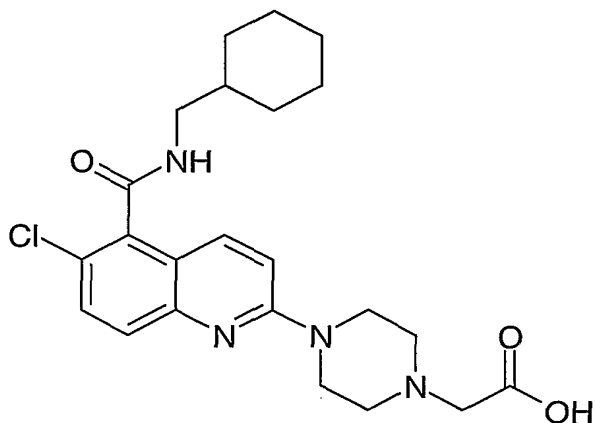
¹H NMR (400 MHz, d₆-DMSO) δ 8.32 (1H, s), 7.81 (1H, d), 7.56-7.46 (2H, m), 6.98 (1H, 15 d), 4.65 (1H, dd), 3.72-3.59 (2H, m), 3.19 (2H, t), 2.36-2.25 (1H, m), 2.16-1.98 (3H, m), 1.84-1.54 (6H, m), 1.34-0.93 (5H, m).

MS: APCI(+ve) 416.1/418.1 (M+H⁺).

m.p. 168-170°C

20 **Example 73**

4-[6-Chloro-5-[[[(cyclohexylmethyl)amino]carbonyl]-2-quinoliny]]-1-piperazineacetic acid, acetate



a) 4-[6-Chloro-5-[(cyclohexylmethyl)amino]carbonyl]-2-quinoliny]-1-piperazineacetic acid, ethyl ester

Prepared according to the method of example 30, using 2,6-dichloro-*N*-(cyclohexylmethyl)-5-quinolinecarboxamide (Example 43(a)) (200 mg) and 1-

5 piperazineacetic acid, ethyl ester (500 mg) to afford the sub-title compound as a solid (200 mg).

¹H NMR (400 MHz, d₆-DMSO) δ 8.63 (1H, t), 7.75 (1H, d), 7.58-7.52 (2H, m), 7.35 (1H, d), 4.15-4.04 (2H, m), 3.77-3.65 (4H, m), 3.20-3.14 (4H, m), 2.66-2.58 (4H, m), 1.84-1.51
10 (6H, m), 1.29-1.09 (6H, m), 1.05-0.90 (2H, m).

MS: APCI(+ve) 473.5/475.5 (M+H⁺).

b) 4-[6-Chloro-5-[(cyclohexylmethyl)amino]carbonyl]-2-quinoliny]-1-piperazineacetic acid, acetate

15 To a stirred suspension of 4-[6-chloro-5-[(cyclohexylmethyl)amino]carbonyl]-2-quinoliny]-1-piperazineacetic acid, ethyl ester (Example 73(a)) (200 mg) in methanol (2 mL) was added sodium hydroxide (2 mL, 1 M solution in water). The mixture was stirred at 50°C for 3 hours and then allowed to cool to room temperature. Reaction mixture was concentrated and then acidified to pH7 with aqueous 2M hydrochloric acid. The resulting
20 precipitate was collected by filtration. Purification (Varian NH₂ cartridge using methanol (100 mL) and then 10 % acetic acid in methanol (100 mL) as eluant) afforded the title compound as a solid (18 mg).

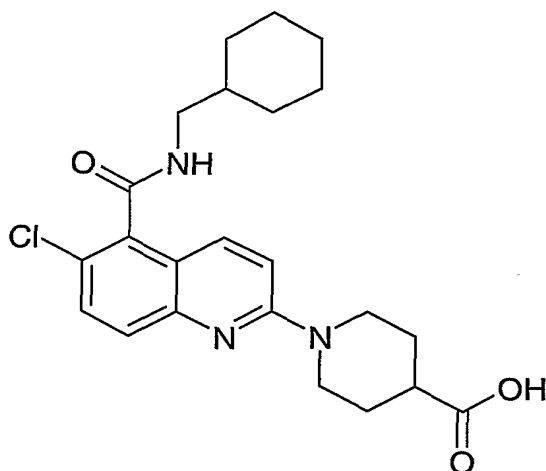
¹H NMR (400 MHz, d₆-DMSO) δ 8.63 (1H, t), 7.75 (1H, d), 7.59-7.50 (2H, m), 7.34 (1H, d), 3.71 (4H, s), 3.22-3.07 (4H, m), 2.63 (4H, s), 1.84-1.50 (6H, m), 1.30-1.10 (3H, m),
25 1.04-0.90 (2H, m).

MS: APCI(-ve) 443.2/445.2 (M-H⁺).

m.p. 185-190°C

30 **Example 74**

1-[6-Chloro-5-[(cyclohexylmethyl)amino]carbonyl]-2-quinoliny]-4-piperidinecarboxylic acid, sodium salt



a) 1-[6-Chloro-5-[(cyclohexylmethyl)amino]carbonyl]-2-quinoliny]-4-piperidinecarboxylic acid, ethyl ester

5 Prepared according to the method of example 30, using 2,6-dichloro-*N*-(cyclohexylmethyl)-5-quinolinecarboxamide (Example 43(a)) (200 mg) and 4-piperidinecarboxylic acid, ethyl ester (470 mg) to afford the sub-titled compound as a solid (200 mg).

10 ¹H NMR (400 MHz, d₆-DMSO) δ 8.62 (1H, t), 7.75 (1H, d), 7.57-7.50 (2H, m), 7.36 (1H, d), 4.43 (2H, d), 4.07 (2H, q), 3.21-3.05 (4H, m), 2.72-2.61 (1H, m), 1.92 (2H, d), 1.85-1.39 (8H, m), 1.28-1.12 (6H, m), 1.03-0.91 (2H, m).

MS: APCI(+ve) 458.5/460.5 (M+H⁺).

15 **b) 1-[6-Chloro-5-[(cyclohexylmethyl)amino]carbonyl]-2-quinoliny]-4-piperidinecarboxylic acid, sodium salt**

Prepared according to the method of example 73(b), using 1-[6-chloro-5-[[cyclohexylmethyl)amino]carbonyl]-2-quinoliny]-4-piperidinecarboxylic acid ethyl ester (Example 74(a)) (200 mg). The reaction mixture was concentrated and the precipitate was
20 collected by filtration and washed with water to afford the title compound as a solid (130 mg).

^1H NMR (400 MHz, d_6 -DMSO) δ 8.62 (1H, t), 7.70 (1H, d), 7.55-7.45 (2H, m), 7.31 (1H, d), 4.29 (2H, d), 3.16 (2H, t), 3.07 (2H, t), 2.12-2.00 (1H, m), 1.85-1.43 (10H, m), 1.28-1.10 (3H, m), 1.04-0.91 (2H, m).

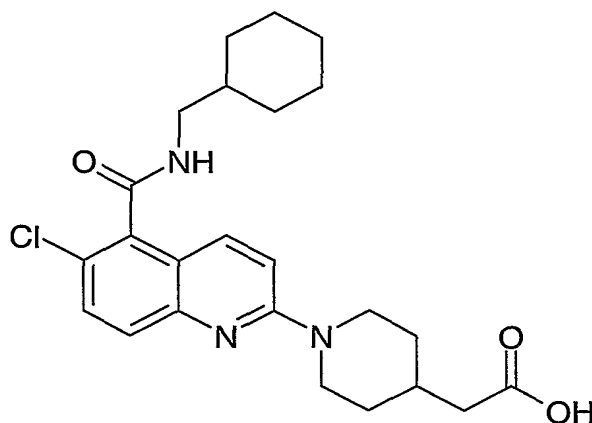
MS: APCI(-ve) 428.2/430.2 ($\text{M}-\text{H}^+$).

5 m.p. 320-324 °C

Example 75

1-[6-Chloro-5-[[cyclohexylmethyl]amino]carbonyl]-2-quinolinyl]-4-piperidineacetic acid, trifluoroacetate

10



a) 1-[6-Chloro-5-[[cyclohexylmethyl]amino]carbonyl]-2-quinolinyl]-4-piperidineacetic acid ethyl ester

Prepared according to the method of example 30, using 2,6-dichloro-*N*

15 (cyclohexylmethyl)-5-quinolinecarboxamide (Example 43(a)) (200 mg) and 4-piperidineacetic acid, ethyl ester (470 mg) to afford the sub-titled compound as a solid (200 mg).

^1H NMR (300 MHz, d_6 -DMSO) δ 8.61 (1H, t), 7.72 (1H, d), 7.52 (2H, s), 7.34 (1H, d),
20 4.52 (2H, d), 4.07 (2H, q), 3.21-3.12 (2H, m), 2.95 (2H, t), 2.26 (2H, d), 2.09-1.93 (1H, m), 1.87-1.48 (8H, m), 1.32-0.88 (10H, m).

MS: APCI(+ve) 472.5/474.5 ($\text{M}+\text{H}^+$).

b) 1-[6-Chloro-5-[[[(cyclohexylmethyl)amino]carbonyl]-2-quinoliny]]-4-piperidineacetic acid, trifluoroacetate

Prepared according to the method of example 73(b), using 1-[6-chloro-5-[[[(cyclohexylmethyl)amino]carbonyl]-2-quinoliny]]-4-piperidineacetic acid ethyl ester (Example 75(a)) (200 mg). Purification by HPLC (Symmetry - 0.1% aqueous trifluoroacetic acid / acetonitrile) afforded the title compound as a solid (90 mg).

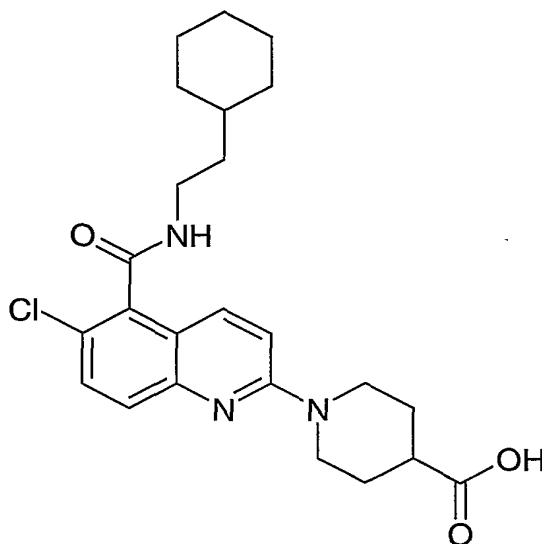
^1H NMR (400 MHz, d_6 -DMSO) δ 8.71 (1H, t), 7.82 (1H, d), 7.77-7.60 (2H, m), 7.50 (1H, d), 4.48 (2H, d), 3.27-3.05 (4H, m), 2.20 (2H, d), 2.11-1.96 (1H, m), 1.88-1.51 (8H, m), 1.35-1.08 (5H, m), 1.05-0.90 (2H, m).

MS: APCI(-ve) 442.2/444.2 (M-H^+).

m.p. 79-83°C

Example 76

1-[6-Chloro-5-[[[(2-cyclohexylethyl)amino]carbonyl]-2-quinoliny]]-4-piperidinecarboxylic acid



a) 5-Bromo-2,6-dichloro-quinoline

2,6-Dichloroquinoline (30 g) and aluminium trichloride (60 g) were heated to 120°C with stirring under a nitrogen atmosphere. Bromine (9.2 mL) was added dropwise over 1 hour

and the mixture was then stirred at 120°C for 1 hour before being cooled to room temperature. A methanol / deionised water mixture (150 mL, 1:1) was then slowly added and the mixture was concentrated *in vacuo*. Dichloromethane (500 mL) and deionised water (250 mL) were added, the layers were separated and the aqueous fraction was
5 extracted with dichloromethane (2 x 250 mL). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (250 mL) before being dried, filtered and concentrated. Purification by chromatography (SiO₂, isohexane: dichloromethane 7:3 as eluant) gave the title compound as a solid (27 g).

10

¹H NMR (400 MHz, CDCl₃) δ 8.53 (1H, d), 7.94 (1H, d), 7.78 (1H, d), 7.50 (1H, d).
MS: APCI(+ve) 276/278/280/282 (M+H⁺).

b) 2,6-Dichloro-5-quinolinecarboxylic acid

15 To a stirred solution of 5-bromo-2,6-dichloro-quinoline (23 g) in tetrahydrofuran (300 mL) at 0°C was added *iso*-propylmagnesium chloride (2M in tetrahydrofuran, 42 mL) over 2 hours. CO₂ was bubbled through the solution for 20 minutes and then methanol (20 mL) was added. The mixture was poured into water (500 mL) and extracted with ethyl acetate. The aqueous layer was acidified with hydrochloric acid (2M in water) to pH2-3 and the
20 resulting solid collected by filtration. The solid was washed with water and dried to afford the sub-titled compound (11.5g).

¹H NMR (400 MHz, d₆-DMSO) δ 8.29 (1H, d), 8.07 (1H, d), 7.94 (1H, d), 7.74 (1H, d).

25 **c) 6-Chloro-2-[4-(ethoxycarbonyl)-1-piperidinyl]-5-quinolinecarboxylic acid**

Prepared according to the method of example 30, using 2,6-dichloro-5-quinolinecarboxylic acid (Example 76(b)) (800 mg) and 4-piperidinecarboxylic acid, ethyl ester (2.7 g). Purification (Varian NH₂ cartridge using methanol (100 mL) and then 2 % acetic acid in methanol (100 mL) as eluant) afforded the title compound as a solid (900 mg).

30

MS: APCI(+ve) 363.2/365.2 (M+H⁺).

d) 1-[6-Chloro-5-[(2-cyclohexylethyl)amino]carbonyl]-2-quinolinyl]-4-piperidinecarboxylic acid ethyl ester

Prepared according to the method of example 4(a), using 6-chloro-2-[4-(ethoxycarbonyl)-1-piperidinyl]-5-quinolinecarboxylic acid (Example 76(c)) (217 mg) and
5 cyclohexaneethanamine (277 mg). Purification (SiO₂, methanol:dichloromethane 1:99 as eluant) gave the title compound as a solid (200 mg).

MS: APCI(+ve) 472.3/474.3 (M+H⁺).

10 **e) 1-[6-Chloro-5-[(2-cyclohexylethyl)amino]carbonyl]-2-quinolinyl]-4-piperidinecarboxylic acid**

To a 10 mL vial was added 1-[6-chloro-5-[(2-cyclohexylethyl)amino]carbonyl]-2-quinolinyl]-4-piperidinecarboxylic acid ethyl ester (Example 76(d)) (200 mg), methanol (2 mL) and potassium hydroxide (100 mg) in water (1 mL). The vial was sealed and heated
15 at 70°C in a microwave for 10 minutes. The mixture was concentrated and the residue was acidified to pH 5 with aqueous 2 M hydrochloric acid. The resulting solid was collected by filtration. Purification (Varian NH₂ cartridge using methanol:dichloromethane 1:1 (100 mL) and then 2 % acetic acid in methanol:dichloromethane 1:1(100 ML) as eluant) afforded the title compound (150 mg).

20 ¹H NMR (400 MHz, d₆-DMSO) δ 8.58 (1H, s), 7.75 (1H, d), 7.61-7.47 (2H, m), 7.35 (1H, d), 4.41 (2H, d), 3.35 (2H, d), 3.09 (2H, t), 2.61-2.41 (1H, m), 1.98-1.85 (2H, m), 1.81-1.33 (10H, m), 1.30-1.06 (3H, m), 1.01-0.82 (2H, m).

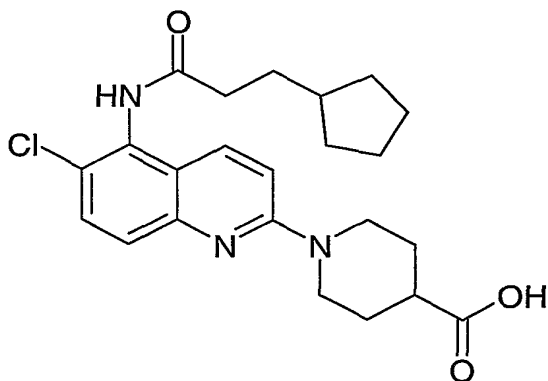
MS: APCI(+ve) 444.1/446.1 (M+H⁺).

25 m.p. 253-256 °C

Example 77

1-[6-Chloro-5-[(3-cyclopentyl-1-oxopropyl)amino]-2-quinolinyl]-4-piperidinecarboxylic acid

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a) 1-(5-Amino-6-chloro-2-quinolinyl)-4-piperidinecarboxylic acid, ethyl ester

Prepared according to the method of example 30, using 2,6-dichloroquinolin-5-amine (Example 1(d)) (800 mg) and 4-piperidinecarboxylic acid, ethyl ester (1.8 g). Purification (SiO₂, methanol:dichloromethane 1:99 as eluant) gave the sub-title compound as a solid (900 mg).

¹H NMR (400 MHz, d₆-DMSO) δ 8.34 (1H, d), 7.29 (1H, d), 7.14 (1H, d), 6.78 (1H, d), 5.84 (2H, s), 4.40 (2H, d), 4.07 (2H, q), 3.03 (2H, t), 2.69-2.58 (1H, m), 1.90 (2H, d), 1.55 (2H, q), 1.19 (3H, t).

MS: APCI(+ve) 334.2/336.2 (M+H⁺).

b) 1-[6-Chloro-5-[(3-cyclopentyl-1-oxopropyl)amino]-2-quinolinyl]-4-piperidinecarboxylic acid, ethyl ester

Prepared according to the method of example 62(a), using cyclopentanepropanoic acid (256 mg) and 1-(5-amino-6-chloro-2-quinolinyl)-4-piperidinecarboxylic acid, ethyl ester (Example 77(a)) (200 mg), to afford the sub-titled compound (240 mg).

¹H NMR (400 MHz, d₆-DMSO) δ 9.80 (1H, s), 7.86 (1H, d), 7.58 (1H, d), 7.49 (1H, d), 7.32 (1H, d), 4.43 (2H, d), 4.08 (2H, q), 3.10 (2H, t), 2.72-2.61 (1H, m), 2.45 (2H, t), 1.98-1.44 (13H, m), 1.24-1.08 (5H, m).

c) 1-[6-Chloro-5-[(3-cyclopentyl-1-oxopropyl)amino]-2-quinolinyl]-4-piperidinecarboxylic acid

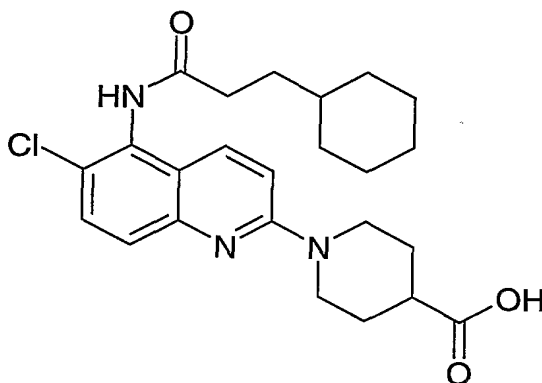
Prepared according to the method of example 73(b), using 1-[6-chloro-5-[(3-cyclopentyl-1-oxopropyl)amino]-2-quinolinyl]-4-piperidinecarboxylic acid, ethyl ester (Example 77(b)) (240 mg), to afford the titled compound (160 mg).

- 5 ^1H NMR (400 MHz, $\text{d}_6\text{-DMSO}$) δ 9.83 (1H, s), 7.84 (1H, d), 7.55 (1H, d), 7.47 (1H, d), 7.29 (1H, d), 4.37 (2H, d), 3.05 (2H, t), 2.45 (2H, t), 2.41-2.32 (1H, m), 1.92-1.75 (5H, m), 1.72-1.45 (8H, m), 1.22-1.08 (2H, m).
MS: APCI(-ve) 428.2/430.2 (M-H^+).

10

Example 78

1-[6-Chloro-5-[(3-cyclohexyl-1-oxopropyl)amino]-2-quinolinyl]-4-piperidinecarboxylic acid, potassium salt



- 15 **a) 1-[6-Chloro-5-[(3-cyclohexyl-1-oxopropyl)amino]-2-quinolinyl]-4-piperidinecarboxylic acid, ethyl ester**

Prepared according to the method of example 62(a), using cyclohexanepropanoic acid (280 mg) and 1-(5-amino-6-chloro-2-quinolinyl)-4-piperidinecarboxylic acid, ethyl ester (Example 77(a)) (200 mg), to afford the sub-titled compound (240 mg).

20

- ^1H NMR (400 MHz, $\text{d}_6\text{-DMSO}$) δ 9.87 (1H, s), 7.98-7.83 (1H, m), 7.72-7.51 (2H, m), 7.43-7.30 (1H, m), 4.43 (2H, d), 4.08 (2H, q), 3.16 (2H, s), 2.76-2.63 (1H, m), 2.46 (2H, t), 1.95 (2H, d), 1.82-1.50 (9H, m), 1.38-1.07 (7H, m), 0.92 (2H, q).
MS: APCI(+ve) 458.2/460.2 (M+H^+).

25

b) 1-[6-Chloro-5-[(3-cyclohexyl-1-oxopropyl)amino]-2-quinolinyl]-4-piperidinecarboxylic acid, potassium salt

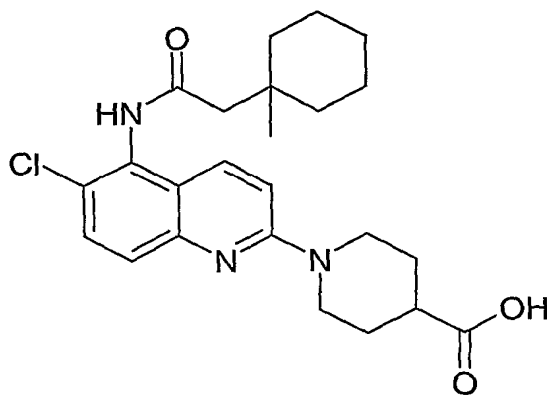
Prepared according to the method of example 76(e), using 1-[6-chloro-5-[(3-cyclohexyl-1-oxopropyl)amino]-2-quinolinyl]-4-piperidinecarboxylic acid, ethyl ester (Example 78(b)) (240 mg). The reaction mixture was concentrated, water was added to the residue and the solid was collected by filtration and washed with water to afford the titled compound (160 mg).

^1H NMR (300 MHz, d_6 -DMSO) δ 9.95 (1H, s), 7.82 (1H, d), 7.53 (1H, d), 7.44 (1H, d), 7.24 (1H, d), 4.27 (2H, d), 3.03 (2H, t), 2.48-2.40 (1H, m), 2.04-1.91 (1H, m), 1.86-1.40 (12H, m), 1.39-1.11 (4H, m), 0.92 (2H, q).

MS: APCI(-ve) 442.2/444.2 (M-H^+).

Example 79

1-[6-Chloro-5-[[1-(1-methylcyclohexyl)acetyl]amino]-2-quinolinyl]-4-piperidinecarboxylic acid



a) 1-[6-Chloro-5-[[1-(1-methylcyclohexyl)acetyl]amino]-2-quinolinyl]-4-piperidinecarboxylic acid, ethyl ester

Prepared according to the method of example 62(a), using 1-methyl-cyclohexaneacetic acid (280 mg) and 1-(5-amino-6-chloro-2-quinolinyl)-4-piperidinecarboxylic acid, ethyl ester (Example 77(a)) (200 mg), to afford the sub-titled compound (200 mg).

MS: APCI(+ve) 472.2/474.2 ($M+H^+$).

b) 1-[6-Chloro-5-[[[(1-methylcyclohexyl)acetyl]amino]-2-quinolinyl]-4-piperidinecarboxylic acid

Prepared according to the method of example 76 (e), using) 1-[6-chloro-5-[[[(1-methylcyclohexyl)acetyl]amino]-2-quinolinyl]-4-piperidinecarboxylic acid, ethyl ester (Example 79(b)) (200 mg). Recrystallisation (ethanol/water) afforded the title compound (160 mg).

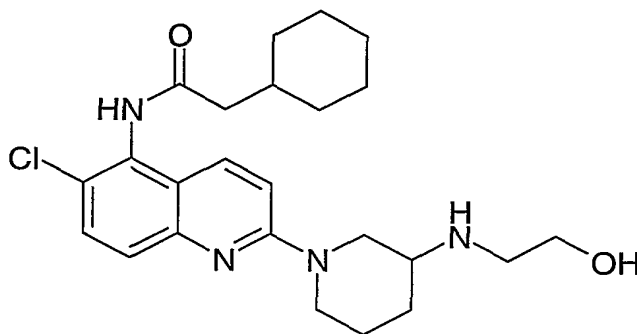
1H NMR (300 MHz, d_6 -DMSO) δ 9.43 (1H, s), 7.91 (1H, d), 7.61-7.45 (2H, m), 7.26 (1H, d), 4.35 (2H, d), 3.17 (2H, t), 2.64-2.52 (1H, m), 2.38 (2H, s), 2.00-1.88 (2H, m), 1.73-1.29 (12H, m), 1.13 (3H, s).

MS: APCI(-ve) 442.2/444.2 ($M-H^+$).

m.p. 210-212°C

Example 80

***N*-[6-Chloro-2-[3-[(2-hydroxyethyl)amino]-1-piperidinyl]-5-quinolinyl]-cyclohexaneacetamide**



a) *N*-[6-Chloro-2-[(3*R*)-3-[(methylsulfonyl)oxy]-1-piperidinyl]-5-quinolinyl]-cyclohexaneacetamide

To a stirred solution of *N*-[6-chloro-2-[(3*R*)-3-hydroxy-1-piperidinyl]-5-quinolinyl]-cyclohexaneacetamide (Example 37) (0.715g) in dichloromethane (10 mL) was added

triethylamine (0.99 mL) followed by methanesulfonyl chloride (0.275 mL). The reaction was stirred under nitrogen for 24 hours followed by the removal of volatiles under vacuum. The resulting mixture was taken up in methanol (20 mL) and placed down a Varian® SCX cartridge, washed with methanol (50 mL) and eluted with ammonia in methanol (0.7M, 50 mL). The solvent was removed to afford the sub-titled compound (0.64 g).

MS: APCI(+ve) 480.4 (M+H⁺).

b) *N*-[6-Chloro-2-[3-[(2-hydroxyethyl)amino]-1-piperidinyl]-5-quinolinyl]-cyclohexaneacetamide

N-[6-Chloro-2-[(3*R*)-3-[(methylsulfonyl)oxy]-1-piperidinyl]-5-quinolinyl]-cyclohexaneacetamide (Example 80(a)) (0.2g), 2-amino-ethanol (0.075ml) and acetonitrile (3ml) were loaded into a 10ml microwave reaction vial, capped and heated at 80 °C for 90 minutes within a single mode microwave. The solvent was removed under vacuum and the residue was purified by chromatography (SiO₂, 7M ammonia in methanol: dichloromethane 1:99 as eluant) to give the title compound as a solid (0.018g).

¹H NMR (400 MHz, CD₃OD) δ 7.91 (1H, d), 7.56 (2H, s), 7.23 (1H, d), 4.60-4.54 (1H, m), 4.31-4.24 (1H, m), 3.68 (2H, t), 3.18-3.10 (1H, m), 2.99-2.92 (1H, m), 2.87-2.82 (2H, m), 2.75-2.67 (1H, m), 2.41 (2H, d), 2.12-2.03 (1H, m), 1.98-1.88 (3H, m), 1.87-1.75 (3H, m), 1.75-1.67 (1H, m), 1.67-1.54 (1H, m), 1.53-1.44 (1H, m), 1.42-1.21 (3H, m), 1.20-1.08 (2H, m).

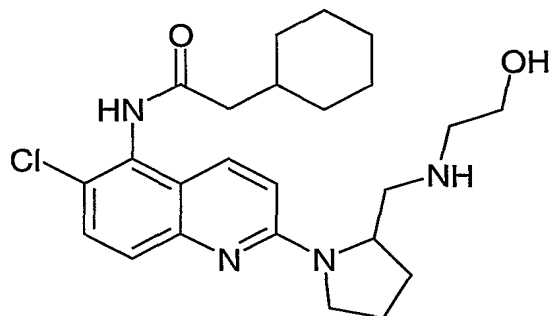
MS: APCI(+ve) 445 (M+H⁺).

m.p. 185-186°C

Example 81

***N*-[6-Chloro-2-[2-[[2-(hydroxyethyl)amino]methyl]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide**

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The title compound was isolated from the previous reaction mixture (Example 80(b)) as a late eluting by-product (30 mg).

5

^1H NMR (400 MHz, CD_3OD) δ 7.93 (1H, d), 7.64 (1H, d), 7.56 (1H, d), 6.99 (1H, d), 4.48-4.41 (1H, m), 3.72-3.66 (3H, m), 3.55-3.47 (1H, m), 3.04-2.98 (1H, m), 2.89-2.76 (3H, m), 2.42 (2H, d), 2.18-1.99 (4H, m), 1.98-1.88 (3H, m), 1.82-1.75 (2H, m), 1.75-1.68 (1H, m), 1.42-1.20 (3H, m), 1.21-1.08 (2H, m).

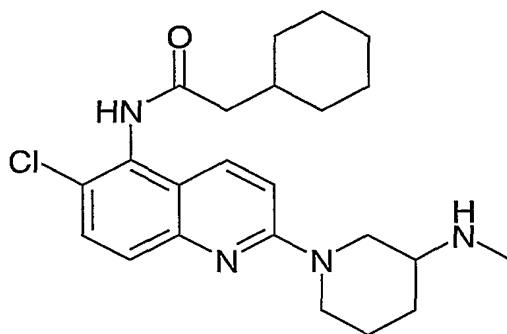
10 MS: APCI(+ve) 445 ($\text{M}+\text{H}^+$).

m.p. 157-158 °C

Example 82

***N*-[6-Chloro-2-[3-(methylamino)-1-piperidinyl]-5-quinolinyl]-cyclohexanecarboxamide**

15



N-[6-Chloro-2-[(3*R*)-3-[(methylsulfonyl)oxy]-1-piperidinyl]-5-quinolinyl]-

cyclohexanecarboxamide (Example 80(a)) (0.2g) and 8M methylamine in ethanol (5ml) were placed into a 10ml microwave vial and heated at 80°C for 60 minutes within a single mode microwave. The reaction was pre-absorbed onto silica and purified (SiO_2 , 7M ammonia in

20

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methanol:methanol:dichloromethane 1:3:96 as eluant). The resulting product was recrystallised from acetonitrile to afford the title compound (0.007g).

^1H NMR (400 MHz, CD_3OD) δ 7.91 (1H, d), 7.56 (2H, s), 7.22 (1H, d), 4.56-4.50 (1H, m),
5 4.28-4.21 (1H, m), 3.20-3.12 (1H, m), 3.02-2.95 (1H, m), 2.63-2.55 (1H, m), 2.46 (3H, s),
2.41 (2H, d), 2.12-2.04 (1H, m), 1.96-1.88 (3H, m), 1.86-1.75 (3H, m), 1.75-1.67 (1H, m),
1.66-1.52 (1H, m), 1.51-1.21 (4H, m), 1.21-1.08 (2H, m).

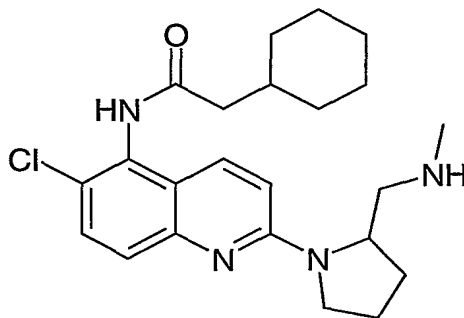
MS: APCI(+ve) 415.2 ($\text{M}+\text{H}^+$).

m.p. 158-159°C

10

Example 83

***N*-[6-Chloro-2-[2-[(methylamino)methyl]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide**



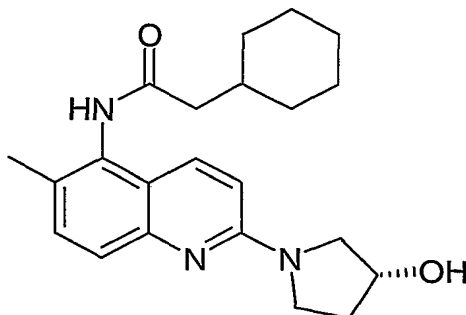
15

The title compound was isolated from the previous reaction mixture (Example 82) as a late eluting by-product (36 mg).

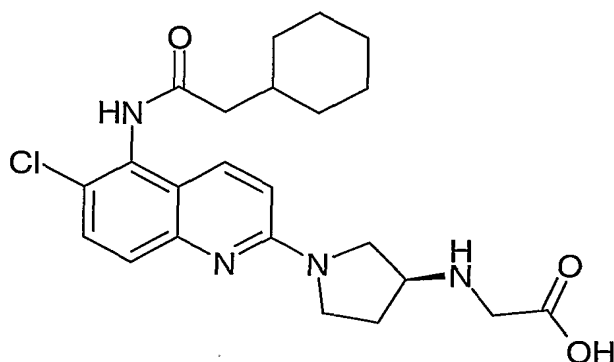
^1H NMR (400 MHz, CD_3OD) δ 7.94 (1H, d), 7.59 (2H, d), 6.99 (1H, d), 4.48 - 4.41 (1H, m),
20 3.72 - 3.67 (1H, m), 3.55 - 3.47 (1H, m), 2.96 (1H, dd), 2.79 (1H, dd), 2.53 (3H, s),
2.42 (2H, d), 2.17 - 2.03 (3H, m), 2.03 - 1.97 (1H, m), 1.97 - 1.88 (3H, m), 1.83 - 1.75 (2H, m),
1.75 - 1.67 (1H, m), 1.42 - 1.21 (3H, m), 1.20 - 1.08 (2H, m).

MS: APCI(+ve) 415.2 ($\text{M}+\text{H}^+$).

25 m.p. 138-145°C

Example 84***N*-[2-[(3*R*)-3-Hydroxy-1-pyrrolidinyl]-6-methyl-5-quinolinyl]-cyclohexaneacetamide**

- 5 Prepared according to the method of example 27, using *N*-(2-chloro-6-methyl-5-quinolinyl)-cyclohexaneacetamide (Example 15(a)) (0.7 g), (3*R*)-3-pyrrolidinol (0.577 g) and acetonitrile (6 mL). Purification (SiO₂, 7M ammonia in methanol:methanol:dichloromethane 1:3:96 as eluant) gave the title compound (0.57g)
- 10 ¹H NMR (400 MHz, CD₃OD) δ 7.95 (1H, d), 7.59 (1H, d), 7.43 (1H, d), 6.89 (1H, d), 4.58-4.53 (1H, m), 3.75-3.68 (3H, m), 3.63-3.57 (1H, m), 2.42 (2H, d), 2.30 (3H, s), 2.22-2.12 (1H, m), 2.11-2.03 (1H, m), 1.99-1.86 (3H, m), 1.83-1.76 (2H, m), 1.75-1.68 (1H, m), 1.43-1.22 (3H, m), 1.22-1.09 (2H, m).
- MS: APCI(+ve) 386.2 (M+H⁺).
- 15 m.p. 248-249 °C

Example 85***N*-[(3*S*)-1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-3-pyrrolidinyl]-glycine**

a) *N*-[(3*S*)-1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinoliny]-3-pyrrolidinyl]-glycine, ethyl ester

N-[2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-chloro-5-quinoliny]-cyclohexaneacetamide

5 (Example 31) (0.25 g), 3 Å molecular sieves (0.2 g) and oxo-acetic acid, ethyl ester (4.9M in toluene) (0.131 mL) were stirred in dichloromethane (5 mL) under nitrogen for 2 hours followed by the addition of sodium triacetoxyborohydride (0.27 g). After 24 hours 1M sodium hydroxide (20 mL) was added with the formation of a precipitate which was filtered and washed with dichloromethane. The organic layer was separated and the
10 aqueous phase extracted twice with dichloromethane. The combined organic phases were washed with brine, dried, filtered and solvent removed under vacuum to afford the subtitled compound (0.1g).

MS: APCI(+ve) 473 (M+H⁺).

15

b) *N*-[(3*S*)-1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinoliny]-3-pyrrolidinyl]-glycine

N-[(3*S*)-1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinoliny]-3-pyrrolidinyl]-glycine

ethyl ester (Example 85(a)) (100 mg), 1M sodium hydroxide (0.422 mL) and methanol (5
20 mL) were stirred for 12 hours before reaction was acidified with 1M hydrochloric acid and volatiles removed under vacuum. Purification (SiO₂, 7M ammonia in methanol:methanol:dichloromethane 1:4:95) gave the title compound (0.028 g)

¹H NMR (400 MHz, CD₃OD plus 1 drop of NaOD (40% in D₂O)) δ 7.95 (1H, d), 7.57
25 (1H, d), 7.52 (1H, d), 6.91 (1H, d), 3.85-3.73 (2H, m), 3.65-3.57 (1H, m), 3.55-3.43 (2H, m), 3.24 (2H, s), 2.40 (2H, d), 2.32-2.23 (1H, m), 2.01-1.89 (4H, m), 1.82-1.74 (2H, m), 1.74-1.67 (1H, m), 1.42-1.20 (3H, m), 1.19-1.08 (2H, m).

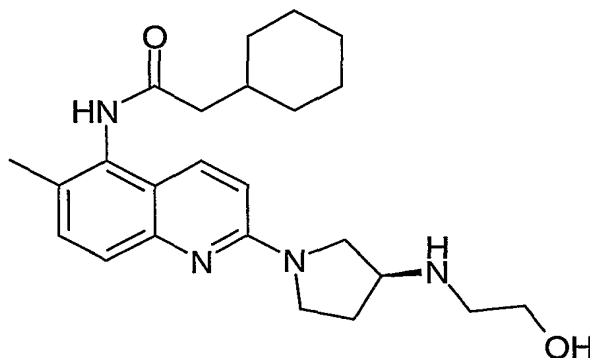
MS: APCI(-ve) 443.4 (M-H⁺).

m.p. 257-259°C

30

Example 86

***N*-[2-[(3*S*)-3-[(2-Hydroxyethyl)amino]-1-pyrrolidinyl]-6-methyl-5-quinolinyl]-cyclohexaneacetamide**



5

a) *N*-[6-Methyl-2-[(3*R*)-3-[(methanesulfonyl)oxy]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide

Prepared according to the method of example 33(a), using *N*-[2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-6-methyl-5-quinolinyl]-cyclohexaneacetamide (Example 84) (0.545 g),
 10 methanesulfonyl chloride (0.23 mL), triethylamine (0.62 mL) and dichloromethane (20 mL) to afford the sub-title compound (0.4 g).

MS: APCI(+ve) 446 ($M+H^+$).

15 b) *N*-[2-[(3*S*)-3-[(2-Hydroxyethyl)amino]-1-pyrrolidinyl]-6-methyl-5-quinolinyl]-cyclohexaneacetamide

Prepared according to the method of example 33(b), using *N*-[6-methyl-2-[(3*R*)-3-[(methanesulfonyl)oxy]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide
 (Example 86(a)) (0.16 g), 2-amino-ethanol (0.065 mL), and acetonitrile (4 mL).
 20 Purification (SiO₂, 7M ammonia in methanol:methanol: dichloromethane 1:2:99 as eluant) gave the title compound (0.06 g).

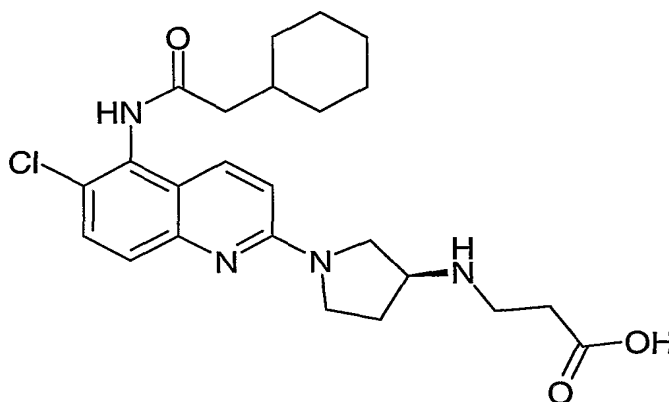
¹H NMR (400 MHz, CD₃OD) δ 7.95 (1H, d), 7.59 (1H, d), 7.43 (1H, d), 6.89 (1H, d), 3.87 (1H, dd), 3.80-3.73 (1H, m), 3.69 (2H, t), 3.64-3.57 (1H, m), 3.53 (1H, quintet), 3.46-3.41 (1H, m), 2.82 (2H, td), 2.41 (2H, d), 2.36-2.26 (1H, m), 2.30 (3H, s), 2.00-1.86 (4H, m),
 25 1.83-1.76 (2H, m), 1.75-1.68 (1H, m), 1.43-1.22 (3H, m), 1.22-1.09 (2H, m)

MS: APCI(+ve) 411.2 ($M+H^+$).

m.p. 204-207 °C

Example 87

5 ***N*-[*(3S)*-1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-3-pyrrolidinyl]- β -alanine**



a) 3-[(3*S*)-3-Pyrrolidinylamino]-propanenitrile

- 10 3-[(3*S*)-1-(Phenylmethyl)-3-pyrrolidinyl]amino]-propanenitrile (as described in WO2000075137) (0.6 g), 20% palladium hydroxide on carbon (0.15 g), 1,4 cyclohexadiene (3 mL) and ethanol (2 mL) were loaded into a 10 mL microwave vial, capped and heated at 100 °C for 90 minutes within a single mode microwave. The reaction mixture was filtered and the volatiles removed under vacuum to afford the sub-title
- 15 compound (0.304 g).

MS: APCI(+ve) 140.3 ($M+H^+$).

b) *N*-[6-Chloro-2-[(3*S*)-3-[(2-cyanoethyl)amino]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide

- 20 *N*-(2,6-Dichloro-5-quinolinyl)-cyclohexaneacetamide (Example 1 (a)) (0.4 g), 3-[(3*S*)-3-pyrrolidinylamino]-propanenitrile (Example 87(a)) (0.3 g) and triethylamine (0.6 mL) were heated within a microwave in a sealed 10 mL vial for 60 minutes at 120 °C. The volatiles were removed under vacuum and the mixture purified (SiO₂, methanol: dichloromethane
- 25 1:99 as eluant) to give the sub-titled compound (0.25 g).

MS: APCI(+ve) 440.5 (M+H⁺).

c) *N*-[(3*S*)-1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-3-pyrrolidinyl]- β -alanine

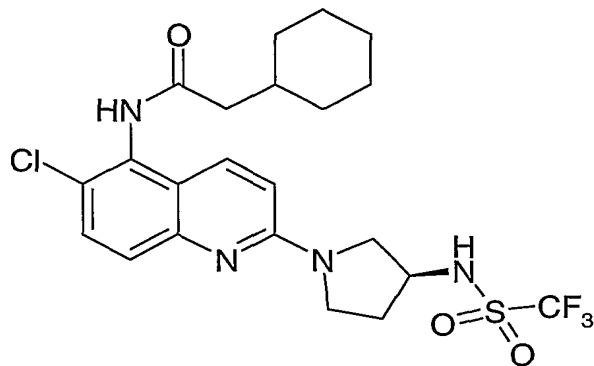
N-[6-Chloro-2-[(3*S*)-3-[(2-cyanoethyl)amino]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide (0.1 g), potassium hydroxide (0.051 g), water (1 mL) and methanol (2 mL) were heated within a single mode microwave in a sealed 10 mL vial for 100 minutes at 90°C. The resulting mixture was dissolved in methanol (20 mL) and purified on a Varian® SCX cartridge, washed with methanol (50 mL) and eluted with ammonia in methanol (0.7M, 50 mL). The residue was further purified on a Varian® NH₂ cartridge washed with methanol (50 mL) and eluted with acetic acid:methanol (10:90). The solvent was removed under vacuum and the residue triturated with hot methanol, cooled and filtered to afford the title compound (7 mg).

¹H NMR (400 MHz, d₆-DMSO) δ 9.76 (1H, s), 7.84 (1H, d), 7.55 (1H, d), 7.47 (1H, d), 6.95 (1H, d), 3.75-3.68 (1H, m), 3.67-3.58 (1H, m), 3.57-3.49 (1H, m), 3.48-3.41 (2H, m), 2.85-2.80 (2H, m), 2.36-2.30 (4H, m), 2.19-2.10 (1H, m), 1.91-1.77 (4H, m), 1.74-1.67 (2H, m), 1.67-1.60 (1H, m), 1.32-1.13 (4H, m), 1.10-0.99 (2H, m).

MS: APCI(-ve) 457.2 (M-H⁺).

Example 88

***N*-[6-Chloro-2-[(3*S*)-3-[(trifluoromethyl)sulfonyl]amino]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide**



N-[2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-chloro-5-quinolinyl]-cyclohexaneacetamide (Example 31) (0.15 g), triethylamine (0.108 mL) and dichloromethane (15 mL) were cooled to 0°C followed by the addition of trifluoroacetic anhydride (0.078 mL). The reaction was allowed to warm to room temperature and stirred for 1 hour. Water (10 mL) was added and the organic phase separated. The combined organic layers were concentrated and the residue purified by HPLC (Symmetry - 0.1% aqueous ammonium acetate / acetonitrile). Further purification on a Varian® NH₂ cartridge, eluting with methanol (50 mL) and then with acetic acid:methanol (10:90), afforded the title product (0.018 g).

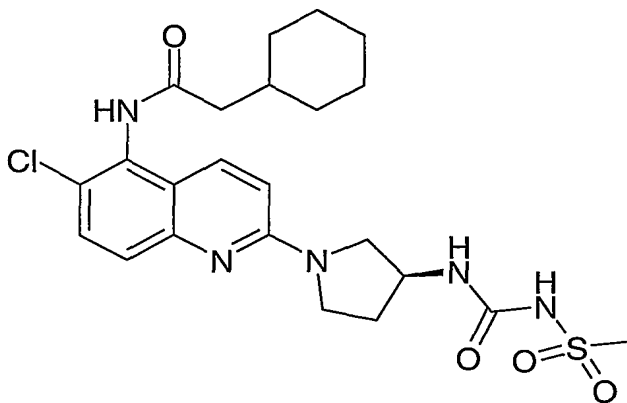
¹H NMR (400 MHz, d₆-DMSO) δ 9.77 (1H, s), 7.85 (1H, d), 7.56 (1H, d), 7.49 (1H, d), 6.96 (1H, d), 4.21-4.13 (1H, m), 3.83-3.75 (1H, m), 3.71-3.63 (1H, m), 3.58-3.50 (1H, m), 3.43-3.35 (1H, m), 2.32 (2H, d), 2.27-2.17 (1H, m), 2.00-1.89 (1H, m), 1.86-1.77 (3H, m), 1.75-1.67 (2H, m), 1.67-1.60 (1H, m), 1.32-1.11 (4H, m), 1.10-0.98 (2H, m).

MS: APCI(+ve) 519.1 (M+H⁺).

m.p. 178-200 °C

Example 89

N-[6-Chloro-2-[(3*S*)-3-[[[(methylsulfonyl)amino]carbonyl]amino]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide



N-[2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-chloro-5-quinolinyl]-cyclohexaneacetamide

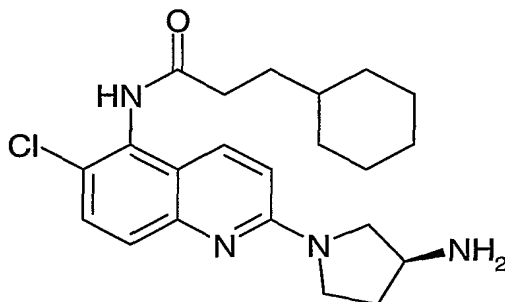
(Example 31) (0.15 g) and (methylsulfonyl)-carbamic acid ethyl ester (0.065 g) were

heated with a single mode microwave in a sealed 10 mL vial for 30 minutes at 130 °C. The residue was purified on a Varian® NH₂ cartridge washed with methanol (50 mL) and eluted with acetic acid:methanol (10:90) to afford the title product (0.016 g).

- 5 ¹H NMR (400 MHz, d₆-DMSO) δ 9.77 (1H, s), 7.86 (1H, d), 7.56 (1H, d), 7.49 (1H, d), 6.97 (1H, d), 6.83-6.76 (1H, m), 4.33-4.25 (1H, m), 3.80-3.74 (1H, m), 3.66-3.55 (2H, m), 3.47-3.39 (1H, m), 3.18 (3H, s), 2.32 (2H, d), 2.27-2.17 (1H, m), 2.01-1.90 (1H, m), 1.88-1.77 (3H, m), 1.75-1.67 (2H, m), 1.67-1.60 (1H, m), 1.32-1.14 (4H, m), 1.13-0.98 (2H, m). MS: APCI(+ve) 508.1 (M+H⁺).
- 10 m.p. 303-307 °C

Example 90

N-[2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-chloro-5-quinolinyl]-cyclohexanepropanamide



15

a) *N*-(2,6-dichloro-5-quinolinyl)-cyclohexanepropanamide

- Prepared according to the method of example 62(a), using 2,6-dichloroquinolin-5-amine (example 1(d)) (0.5 g) and cyclohexanepropionic acid (1.2 mL). The resulting precipitate was filtered and washed with acetone. The precipitate was further washed with water and then ether to give the sub-title compound as a solid (0.248 g)
- 20

¹H NMR (300 MHz, DMSO) δ 8.28-8.25 (1H, d), 7.93 (2H, s), 7.69-7.66 (1H, d), 1.78-1.53 (8H, m), 1.31-1.12 (5H, m), 0.98-0.86 (2H, m).

- 25 MS: APCI(+ve) 351.2 (M+H⁺).

b) *N*-[2-(3-Amino-1-pyrrolidinyl)-6-chloro-5-quinolinyl]-cyclohexanepropanamide

N-(2,6-Dichloro-5-quinolinyl)-cyclohexanepropanamide (Example 90(a)) (0.24 g), (S)-3-aminopyrrolidine (0.18 g) and triethylamine (0.1 mL) were suspended in acetonitrile and heated at 100°C in a microwave for 1 hour. The resulting precipitate was filtered and then washed with acetonitrile to give a brown solid. Purification (SiO₂,

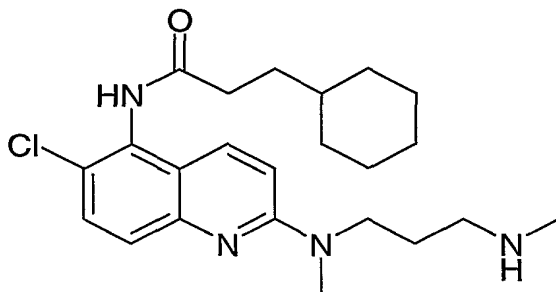
methanol:dichloromethane:triethylamine 3:97:0.5) gave the title compound as a colourless solid (230 mg).

¹H NMR (400 MHz, DMSO) δ 9.77 (1H, s), 7.86-7.83 (1H, d), 7.56-7.54 (1H, d), 7.48-7.46 (1H, d), 6.93-6.91 (1H, d), 3.70-3.64 (3H, m), 3.56-3.55 (1H, m), 2.46-2.42 (2H, t), 2.16-2.14 (1H, m), 1.85-1.53 (8H, m), 1.32-1.1 (5H, m), 0.96-0.85 (2H, m).

MS: APCI(+ve) 401.2 (M+H⁺)

Example 91

N-[6-Chloro-2-[methyl[3-(methylamino)propyl]amino]-5-quinolinyl]-cyclohexanepropanamide



Prepared according to the method of example 90(b), using *N*-(2,6-dichloro-5-quinolinyl)-cyclohexanepropanamide (Example 90(a)) (0.16 g), *N,N'*-dimethylpropanediamine (0.3 mL) and triethylamine (0.1 mL). Purification (SiO₂, methanol:dichloromethane:triethylamine 5:95:0.5 followed by HPLC, Symmetry - 0.1% aqueous trifluoroacetic acid:acetonitrile) gave the title compound as a solid (70 mg).

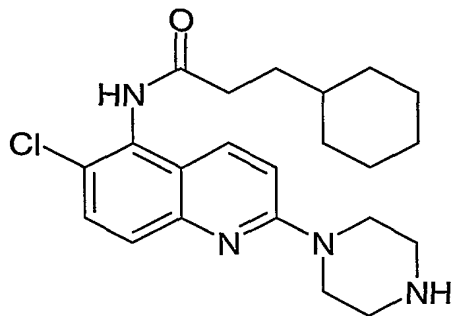
¹H NMR (400 MHz, d₆-DMSO) δ 9.85(1H, s), 8.43 (2H, bs), 7.91-7.89 (1H, d), 7.65-7.63 (1H, d), 7.59 (1H, bs), 7.22-7.2 (1H, d), 3.77-3.74 (1H, t), 2.93-2.91 (1H, t), 2.58-2.55 (2H,

t), 2.52 (6H, m), 2.48-2.44 (2H, t), 1.96-1.93 (2H, t), 1.89-1.62 (5H, m), 1.59-1.53 (2H, q), 1.33-1.10 (4H, m), 0.96-0.85 (2H, m).

MS: APCI(+ve) 417.2 ($M+H^+$).

5 Example 92

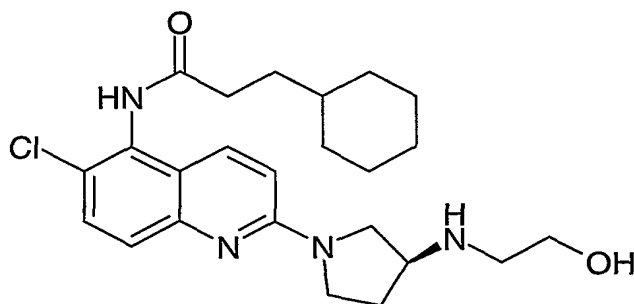
N-[6-Chloro-2-(1-piperazinyl)-5-quinolinyl]-cyclohexanepropanamide



10 *N*-(2,6-Dichloro-5-quinolinyl)-cyclohexanepropanamide (Example 90(a)) (0.16 g), 1-piperazinecarboxylic acid, 1,1-dimethylethyl ester (0.34 g), triethylamine (0.15 mL) and *tetra*-butylammonium bromide (80 mg) were heated at 140°C for 1 hour in a microwave. The resulting precipitate was filtered and then washed with acetonitrile to give a solid. This solid was dissolved in dichloromethane and trifluoroacetic acid (1 mL) was added. The reaction mixture was stirred at room temperature for 3 hours, then concentrated under
15 vacuum to dryness. Purification (HPLC, Symmetry - 0.1% aqueous trifluoroacetic acid:acetonitrile followed by Varian SCX cartridge using methanol and then 10% ammonia in methanol as eluant) gave the title compound as a white solid (30 mg).

20 ^1H NMR (400 MHz, DMSO) δ 9.79 (1H, s), 7.86-7.83 (1H, d), 7.58-7.56 (1H, d), 7.48-7.46 (2H, d), 7.28-7.26 (1H, d), 3.61 (4H, t), 2.8 (4H, m), 2.49-2.42 (2H, t), 1.79-1.53 (7H, m), 1.36-1.1 (4H, m), 0.96-0.85 (2H, m).

MS: APCI(+ve) 401.2 ($M+H^+$).

Example 93***N*-[6-Chloro-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexanepropanamide**

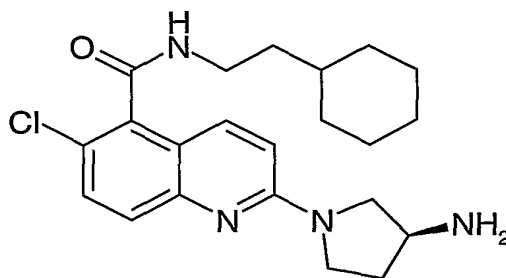
Prepared according to method of example 50(a), using *N*-[2-(3-amino-1-pyrrolidinyl)-6-chloro-5-quinolinyl]-cyclohexanepropanamide (Example 90(b)) (0.12 g), (*tert*-butyldimethylsilyloxy)acetaldehyde (51 μ L) and sodium triacetoxyborohydride (0.13 g). The crude mixture was purified (SiO_2 , methanol:dichloromethane 2:98) and the product dissolved in dichloromethane. Trifluoroacetic acid (0.2 mL) was added and the reaction mixture stirred at room temperature for 48 hours. The reaction mixture was concentrated under vacuum and the residue purified (Varian SCX cartridge using methanol and then 10% ammonia in methanol, HPLC Symmetry, 0.1% aqueous ammonium acetate:acetonitrile) to give the title compound as a solid (0.018 g).

^1H NMR (400 MHz, d_6 -DMSO) δ 9.76 (1H, s), 7.84-7.82 (1H, d), 7.55-7.52 (1H, d), 7.47-7.45 (1H, d), 6.92-6.90 (1H, d), 3.6-3.4 (6H, m), 2.6 (2H, m), 2.46-2.42 (2H, t), 2.15-2.07 (1H, m), 1.89-1.53 (8H, m), 1.36-1.1 (5H, m), 0.96-0.83 (2H, m).

MS: APCI(+ve) 445.2 ($\text{M}+\text{H}^+$).

Example 94**2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-chloro-*N*-(2-cyclohexylethyl)-5-quinolinecarboxamide, ditrifluoroacetate**

163

**a) 6-Chloro-5-quinolinecarboxylic acid**

tert-Butyllithium (1.6 mL, 1.7 M in pentane) was added to a solution of 5-bromo-6-chloro-quinoline (prepared according to the method of Journal of Heterocyclic Chemistry 1967, **4**, 410) (0.3 g) in dry tetrahydrofuran at -78°C under nitrogen. The reaction mixture was stirred at -78°C for 10 minutes and then carbon dioxide bubbled through for one minute. The reaction mixture was stirred at -78°C for another 10 minutes and then water (3 mL) added. The reaction mixture was allowed to warm up to room temperature, concentrated under vacuum and the residue was partitioned between water and ethyl acetate. The aqueous layer was freeze dried to give the sub-titled compound as a solid (0.3 g).

¹H NMR (300 MHz, d₆-DMSO) δ 8.84-8.82 (1H, d), 8.29-8.27 (1H, d), 7.77-7.74 (1H, d), 7.61-7.58 (1H, d), 7.51-7.47 (1H, m).

MS: APCI(+ve) 208 (M+H⁺).

b) 6-Chloro-N-(2-cyclohexylethyl)-5-quinolinecarboxamide

Oxalyl chloride (0.3 mL) was added to a suspension of 6-chloro-5-quinolinecarboxylic acid (example 94(a)) (0.3 g) in dichloromethane and 2 drops of *N,N'*-dimethylformamide. The reaction mixture was stirred at room temperature for 1 hour then evaporated to an oil. The residue was added to cyclohexylethylamine hydrochloride (0.33 g) and triethylamine (0.6 mL) in dichloromethane and then stirred at room temperature for 1 hour. Water was added and the reaction mixture was extracted with dichloromethane. The combined organics were dried and concentrated. Purification (SiO₂, ethyl acetate:isohexane 50:50) gave the sub titled compound as a solid (0.115 g).

¹H NMR (300 MHz, d₆-DMSO) δ 8.97-8.96 (1H, m), 8.73-8.70 (1H, t), 8.11-8.04 (2H, m), 7.84-7.81 (1H, d), 7.67-7.63 (1H, m), 3.39-3.36 (2H, q), 1.76-1.62 (5H, m), 1.50-1.35 (3H, m), 1.30-1.07 (3H, m), 0.96-0.85 (2H, m).

MS: APCI(+ve) 317.3 (M+H⁺).

5

c) 6-Chloro-5-[[2-cyclohexylethyl]amino]carbonyl]-1-hydroxy- quinolinium

Peracetic acid (1.3 mL, 36-40% in acetic acid) was added to 6-chloro-*N*-(2-cyclohexylethyl)-5-quinolinecarboxamide (Example 94(b)) (0.115 g) in acetic acid and the reaction mixture stirred at room temperature overnight. The reaction mixture was washed with a 10% sodium sulfite solution and then extracted with dichloromethane. The organics were washed with water, dried and concentrated. Purification (SiO₂, methanol:ethylacetate 5:95) gave the sub titled compound as a solid (0.05 g).

10

¹H NMR (300 MHz, d₆-DMSO) δ 8.80-8.77 (1H, t), 8.64-8.63 (1H, d), 8.57-8.55 (1H, d), 7.89-7.86 (1H, d), 7.61-7.55 (2H, m), 3.4 (2H, q), 1.90-1.62 (5H, m), 1.50-1.35 (3H, m), 1.25-1.09 (3H, m), 0.96-0.85 (2H, m).

15

MS: APCI(+ve) 333.3 (M+H⁺).

d) 2,6-Dichloro-*N*-(2-cyclohexylethyl)-5-quinolinecarboxamide

Phosphorous oxychloride (2 mL) was added to 6-chloro-5-[[2-cyclohexylethyl]amino]carbonyl]-1-hydroxy-quinolinium (Example 94(c)) (0.089g) and the mixture heated at 60°C for 2 hours. The reaction mixture was concentrated under reduced pressure and added to water. The aqueous was extracted with ethyl acetate and the combined organics dried filtered and evaporated give the sub titled compound as a solid (0.079 g).

20

25

MS: APCI(+ve) 351.4 (M+H⁺).

e) 2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-chloro-*N*-(2-cyclohexylethyl)- 5-quinolinecarboxamide, ditrifluoroacetate

30

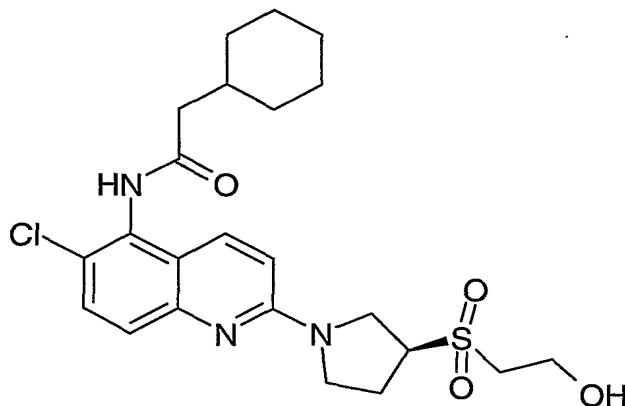
Prepared according to the method of example 90(b), using 2,6-dichloro-*N*-(2-cyclohexylethyl)-5-quinolinecarboxamide (Example 94(d)) (0.079 g), (3*S*)-3-

aminopyrrolidine (0.05 g) and triethylamine (0.031 mL). The reaction mixture was concentrated under reduced pressure and purified (HPLC Symmetry, 0.1% aqueous trifluoroacetic acid:acetonitrile as eluant) to give the title compound (0.014 g).

- 5 ^1H NMR (300 MHz, d_6 -DMSO) δ 8.65 (1H, bs), 8.11 (3H, bs), 7.84-7.82(1H, d), 7.65-7.62 (2H, m), 7.11-7.09 (1H, d), 4.12-3.56(4H, range of ppm), 3.36-3.34(2H, d), 2.38-2.32(1H, m), 2.14(1H, m), 1.76-1.64(5H, m), 1.46-1.4(3H, m), 1.23-1.12(4H, m), 0.93-0.90(2H, m). MS: APCI(+ve) 401.2 ($\text{M}+\text{H}^+$).

10 **Example 95**

***N*-[6-Chloro-2-[(3*S*)-3-[(2-hydroxyethyl)sulfonyl]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide**



- 15 **a) *N*-[6-Chloro-2-[(3*S*)-3-[(2-hydroxyethyl)thio]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide**

Mercaptoethanol (0.073 mL) was added to *N*-[6-chloro-2-[(3*S*)-3-[(methylsulfonyl)oxy]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide (Example 33(a)) (0.1 g) and potassium carbonate (0.24 g) in dry *N,N*-dimethylformamide. The reaction mixture was heated at 60°C in a microwave for 2 hours and then partitioned between water and ethyl acetate. The combined organics were washed with brine, dried and concentrated. Purification (SiO_2 , methanol:dichloromethane 3:97 as eluant) gave the sub-titled compound as a solid (0.05 g).

20

MS: APCI(+ve) 448.1 ($\text{M}+\text{H}^+$).

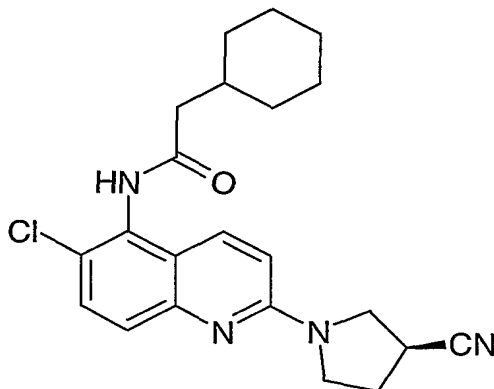
b) *N*-[6-Chloro-2-[(3*S*)-3-[(2-hydroxyethyl)sulfonyl]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide

Hydrogen peroxide (0.57 mL, 1.25M in methanol) and *p*-toluenesulfonylimidazole (0.081 g) were added to *N*-[6-chloro-2-[(3*S*)-3-[(2-hydroxyethyl)thio]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide (Example 95(a)) (0.034 g) in methanol. The reaction mixture was cooled down to 0°C and 1M sodium hydroxide (0.36 mL) was carefully added. The reaction mixture was allowed to warm up to room temperature overnight and 10 mL of 10% sodium metabisulfite solution added. Methanol was removed under reduced pressure and the aqueous layer extracted with dichloromethane. The combined organics were concentrated under vacuum. Purification (SiO₂, methanol:dichloromethane 2:98 as eluant) gave the title compound as a solid (0.004 g).

¹H NMR (300 MHz, d₆-DMSO) δ 9.78 (1H, s), 7.90-7.87 (1H, d), 7.60-7.57 (1H, d), 7.53-7.50 (1H, d), 7.04-7.00 (1H, d), 5.22-5.18 (1H, t), 4.19-4.14 (1H, q), 3.87-3.60 (7H, m), 3.37-3.33 (1H, m), 2.4 (2H, m), 2.33-2.31 (2H, d), 1.83-1.62 (6H, m), 1.29-1.02 (5H, m). MS: APCI(+ve) 480.1 (M+H⁺).

Example 96

***N*-[6-Chloro-2-[(3*S*)-3-cyano-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide**



Lithium cyanide (4 mL, 0.5M in DMF) was added to *N*-[6-chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide (Example 33(a)) (0.21 g) in *N,N'*-dimethylformamide. The reaction mixture was heated at 60°C for 10 hours. A saturated solution of sodium bicarbonate was added and the reaction mixture extracted with ethyl

acetate. The combined organics were washed with brine, dried and concentrated.

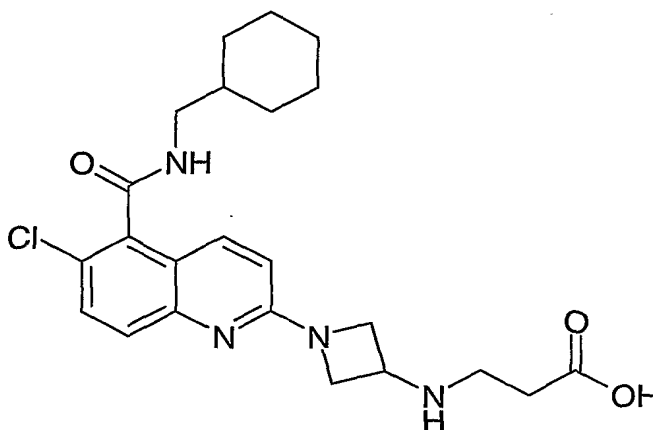
Purification (SiO₂, *iso*-hexane:ethyl acetate 1:1 as eluant) gave the title compound as a solid (0.066 g).

- 5 ¹H NMR (300 MHz, d₆-DMSO) δ 9.78 (1H, s), 7.90-7.87 (1H, d), 7.60-7.57 (1H, d), 7.53-7.50 (1H, d), 7.02-6.99 (1H, d), 3.92-3.57 (5H, m), 2.44-2.25 (4H, m), 1.83-1.62 (6H, m), 1.29-1.02 (5H, m).

MS: APCI(+ve) 397.1 (M+H⁺).

10 **Example 97**

***N*-[1-[6-Chloro-5-[[*(cyclohexylmethyl)*amino]carbonyl]-2-quinolinyl]-3-azetidiny]-β-alanine**



- 15 **a) 2-(3-Amino-1-azetidiny)-6-chloro-*N*-(cyclohexylmethyl)-5-quinolinecarboxamide**
3-Azetidinyl-carbamic acid, 1,1-dimethylethyl ester (0.5 g) was added to 2,6-dichloro-*N*-(cyclohexylmethyl)quinoline-5-carboxamide (Example 43(a)) (0.28 g), *tetra*-butylammonium bromide (0.28 g) and triethylamine (0.5 mL) in acetonitrile (4 mL). The reaction mixture was heated at 120°C in a microwave for 1 hour, concentrated under
20 reduced pressure and purified (SiO₂, methanol:dichloromethane 4:96 as eluant). The residue (0.24 g) was dissolved in dichloromethane and trifluoroacetic acid (1 mL) added. The reaction mixture was stirred at room temperature for 1 hour, concentrated and then treated with 7M ammonia in methanol. Purification (Varian SCX cartridge using methanol and then 10% ammonia in methanol) gave the sub-titled compound as a solid (0.1 g).

¹H NMR (400 MHz, d₆-DMSO) δ 8.64-8.60 (1H, t), 7.73-7.70 (1H, d), 7.57-7.57 (2H, m), 6.82-6.79 (1H, d), 4.28-4.23 (2H, t), 3.89-3.80 (1H, q), 3.71-3.66 (2H, m), 3.18-3.14 (2H, t), 1.80-1.34 (6H, m), 1.28-0.91 (5H, m).

5

b) *N*-[1-[6-Chloro-5-[(cyclohexylmethyl)amino]carbonyl]-2-quinolinyl]-3-azetidiny]- β -alanine

To a stirred solution of 2-(3-amino-1-azetidiny)-6-chloro-*N*-(cyclohexylmethyl)-5-quinolinecarboxamide (Example 97(a)) (0.1 g) in methanol (1 mL) was added ethyl acrylate (0.032 mL). The mixture was stirred at room temperature for 20 hours. Sodium hydroxide (1 mL, 1M) was added and the reaction mixture was stirred for 72 hours. Hydrochloric acid (0.5 mL, 2M) was added and the reaction mixture was concentrated under vacuum. Purification (HPLC - Symmetry, 0.1% aqueous ammonium acetate: acetonitrile as eluant) gave the title compound as a solid (0.026 g).

15

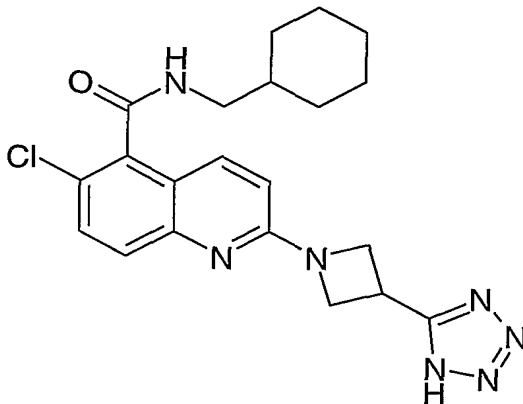
¹H NMR (400 MHz, d₆-DMSO) δ 8.64-8.60 (1H, t), 7.74-7.71 (1H, d), 7.57-7.49 (2H, m), 6.82-6.79 (1H, d), 4.26-4.21 (2H, t), 3.78-3.68 (3H, m), 3.18-3.13 (2H, t), 2.74-2.69 (2H, t), 2.34-2.27 (2H, m), 1.80-1.60 (6H, m), 1.23-0.85 (5H, m).

MS: APCI(-ve) 443.2 (M-H⁺).

20

Example 98

6-Chloro-*N*-(cyclohexylmethyl)-2-[3-(1*H*-tetrazol-5-yl)-1-azetidiny]-5-quinolinecarboxamide



25

a) 6-Chloro-2-(3-cyano-1-azetidiny)-N-(cyclohexylmethyl)-5-quinolinecarboxamide

A mixture of 2,6-dichloro-*N*-(cyclohexylmethyl)-5-quinolinecarboxamide (example 43(a)) (0.25 g, 0.74 mmol), 3-azetidinecarbonitrile (prepared according to the method of JP 2001172257A), *tetra*-butylammonium bromide (0.25 g) and potassium carbonate (0.2 g) in *N*-methylpyrrolidinone were heated at 130°C in a microwave for 2 hours. Water was added and the reaction mixture was extracted with dichloromethane. The organic fraction was washed with water, dried over magnesium sulfate and concentrated. The residue was purified firstly by C18 cartridge (eluting with 10 to 100% methanol in water) and then by chromatography (SiO₂, ethyl acetate:methanol 100:0 to 50:50 as eluant) to give the sub-
title compound as a solid (0.082 g).

MS: APCI(+ve) 383.2 (M+H⁺).

b) 6-Chloro-N-(cyclohexylmethyl)-2-[3-(1*H*-tetrazol-5-yl)-1-azetidiny]-5-quinolinecarboxamide

To a stirred solution of 6-chloro-2-(3-cyano-1-azetidiny)-*N*-(cyclohexylmethyl)-5-quinolinecarboxamide (Example 98(a)) (0.08 g) and dibutyltin oxide (0.017 g) in toluene (5 mL) was added azidotrimethylsilane (0.08 mL). The mixture was heated at 100°C for 20 hours after which it was cooled and then methanol added. The solvent was evaporated under reduced pressure, methanol was added and the mixture stirred for 5 minutes before being concentrated under vacuum. The residue was purified (HPLC, Symmetry - 0.1% aqueous trifluoroacetic acid:acetonitrile) to give the title compound as a solid (0.033 g).

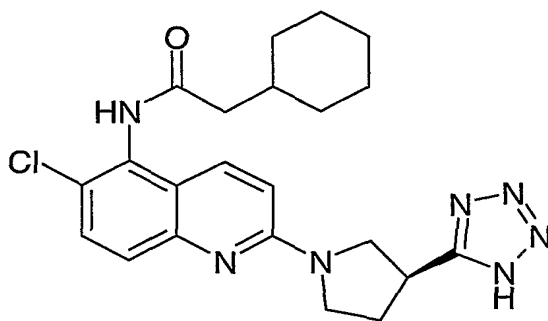
¹H NMR (400 MHz, d₆-DMSO) δ 10.51 (1H, s), 8.88-8.87 (1H, t), 8.06-8.03 (1H, d), 7.95-7.91 (2H, m), 7.18 (1H, d), 4.80 (2H, m), 4.20 (1H, m), 4.00 (1H, m), 3.85-3.81 (1H, m), 3.19-3.16 (2H, q), 1.79-1.54 (6H, m), 1.24-0.93 (5H, m).

MS: APCI(+ve) 426.1 (M+H⁺).

Example 99

***N*-[6-Chloro-2-[(3*S*)-3-(1*H*-tetrazol-5-yl)-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide**

170



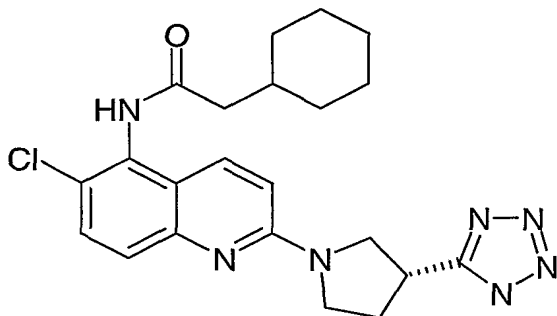
Prepared according to the method of example 98(b), using *N*-[6-chloro-2-[(3*S*)-3-cyano-1-pyrrolidinyl]-5-quinolinyl]-cyclohexanecarboxamide (example 96) (0.036 g). Purification (Varian NH₂ cartridge, methanol then 2% acetic acid in methanol as eluant) gave the title compound as a solid (0.028 g).

¹H NMR (300 MHz, d₆-DMSO) δ 9.77 (1H, s), 7.88-7.85 (1H, d), 7.58-7.55 (1H, d), 7.50-7.47 (1H, d), 7.01-6.98 (1H, d), 4.10-3.61 (5H, m), 2.33-2.25 (3H, m), 1.91-0.98 (11H, m), 0.87-0.82 (1H, t).

MS: APCI(+ve) 440.1 (M+H⁺).

Example 100

N-[6-Chloro-2-[(3*R*)-3-(1*H*-tetrazol-5-yl)-1-pyrrolidinyl]-5-quinolinyl]-cyclohexanecarboxamide



a) *N*-[6-Chloro-2-[(3*R*)-3-cyano-1-pyrrolidinyl]-5-quinolinyl]-cyclohexanecarboxamide

Prepared according to the method of example 96, using *N*-[6-chloro-2-[(3*S*)-3-[(methylsulfonyl)oxy]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexanecarboxamide (example 33

(a)) (0.33 g) and lithium cyanide in *N,N*-dimethylformamide (6 mL, 0.5M). Purification (SiO₂, *isohexane*:ethyl acetate 60:40, as eluant) gave the sub-title compound as a solid (0.066 g).

5 ¹H NMR (300 MHz, d₆-DMSO) δ 9.79 (1H, d), 7.91-7.88 (1H, d), 7.61-7.58 (1H, d), 7.53-7.55 (1H, d), 7.03-7.00 (1H, d), 3.90-3.57 (5H, m), 2.44-2.20 (4H, m), 1.83-1.63 (6H, m), 1.29-0.90 (5H, m).

MS: APCI(+ve) 397.5 (M+H⁺).

10 **b) *N*-[6-Chloro-2-[(3*R*)-3-(1*H*-tetrazol-5-yl)-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide**

Prepared according to the method of example 98 (b), using *N*-[6-chloro-2-[(3*R*)-3-cyano-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide (example 100 (a)) (66 mg), dibutyltin oxide (9 mg) and azidotrimethylsilane (0.06 mL). The residue was purified by ion

15 exchange column (Varian NH₂ cartridge, methanol then 3% acetic acid in methanol as eluant). Further purification by ion exchange column (Varian SCX cartridge, methanol then 7N ammonia in methanol as eluant) gave the title compound as a solid (11 mg).

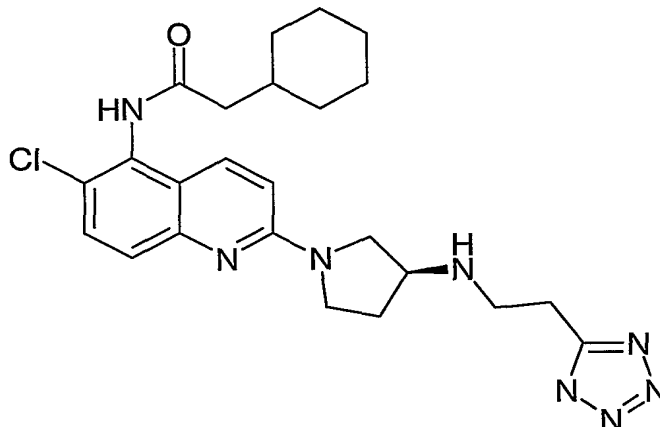
¹H NMR (400 MHz, CD₃OD) δ 9.78 (1H, s), 7.89-7.86 (1H, d), 7.58-7.56 (1H, d), 7.50-7.49 (1H, d), 7.01-6.99 (1H, d), 4.20-3.60 (5H, m), 2.29-2.25 (3H, m), 1.86-1.57 (6H, m), 1.31-0.99 (6H, m).

MS: APCI(+ve) 440.1 (M+H⁺).

Example 101

25 ***N*-[6-Chloro-2-[(3*S*)-3-[[2-(2*H*-tetrazol-5-yl)ethyl]amino]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide**

172



N-[6-Chloro-2-[(3*S*)-3-[(2-cyanoethyl)amino]-1-pyrrolidinyl]-5-quinoliny]-cyclohexaneacetamide (example 87 (b)) (0.15 g), trimethylsilylazide (0.091ml), dibutyltin oxide (0.009g) and toluene (5ml) were heated within a single mode microwave in a sealed 10ml vial at 100 °C for 30 minutes and then at 120 °C for 120 minutes. The reaction was cooled to room temperature, filtered and washed with toluene. The solid was then triturated with methanol and filtered before being dissolved in hot methanol and purified by Varian SCX cartridge (methanol (50ml) and then ammonia in methanol (0.7M, 50ml) as eluant). to afford the title compound (0.025g).

¹H NMR (400 MHz, d₆-DMSO) δ 9.78 (1H, s), 7.86 (1H, d), 7.57 (1H, d), 7.49 (1H, d), 6.98 (1H, d), 3.85 - 3.62 (3H, m), 3.61 - 3.49 (2H, m), 3.19 - 3.12 (2H, m), 3.07 - 3.00 (2H, m), 2.32 (2H, d), 2.30 - 2.19 (1H, m), 2.09 - 1.96 (1H, m), 1.89 - 1.76 (3H, m), 1.76 - 1.59 (3H, m), 1.35 - 1.13 (3H, m), 1.12 - 0.97 (2H, m).

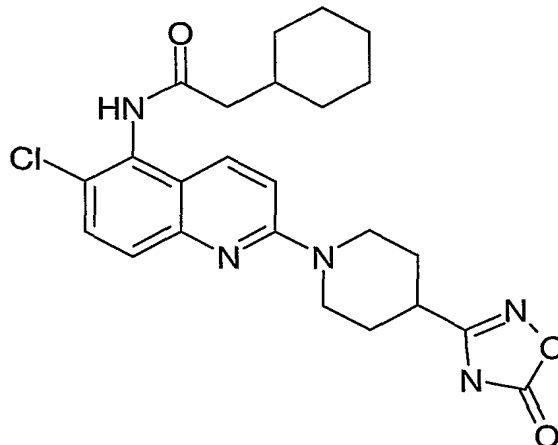
MS: APCI(+ve) 483.5 (M+H⁺).

m.p. 220-221 °C

Example 102

N-[6-Chloro-2-[4-(4,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)-1-piperidinyl]-5-quinoliny]-cyclohexaneacetamide

173



a) *N*-[2-[4-[Amino(hydroxyimino)methyl]-1-piperidinyl]-6-chloro-5-quinolinyl]-cyclohexaneacetamide

5 *N*-[6-Chloro-2-(4-cyano-1-piperidinyl)-5-quinolinyl]-cyclohexaneacetamide (Example 113) (0.2g), hydroxylamine (50% w/v in H₂O) (0.23 mL) and ethanol (2.5 mL) were heated within a microwave in a sealed 10 mL vial at 90 °C for 100 minutes. The reaction was cooled to room temperature and the resulting precipitate was filtered and washed with ethanol to afford the sub-title compound as a solid (0.18 g).

10

¹H NMR (400 MHz, d₆-DMSO) δ 9.77 (1H, s), 8.79 (1H, s), 7.84 (1H, d), 7.56 (1H, d), 7.48 (1H, d), 7.33 (1H, d), 5.33 (2H, s), 4.58 (2H, d), 2.93 (2H, t), 2.36-2.27 (3H, m), 1.87-1.76 (5H, m), 1.75-1.67 (2H, m), 1.66-1.53 (3H, m), 1.32-1.12 (3H, m), 1.10-0.98 (2H, m). MS: APCI(+ve) 444 (M+H⁺).

15 m.p. 246-247 °C

b) *N*-[6-Chloro-2-[4-(4,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)-1-piperidinyl]-5-quinolinyl]-cyclohexaneacetamide

To a stirred solution of *N*-[2-[4-[amino(hydroxyimino)methyl]-1-piperidinyl]-6-chloro-5-quinolinyl]-cyclohexaneacetamide (example 102(a)) (0.1 g) and pyridine (0.02 mL) in dichloromethane (5 mL) at 0 °C was added 2-ethylhexylchloroformate (0.064 mL). After 20 10 minutes the reaction was allowed to warm to room temperature and was then stirred for 2 hours. The solvent was removed under vacuum and the resulting solid was transferred to a 10 mL microwave vial with *iso*hexane (3 mL) and heated within a microwave at 140 °C

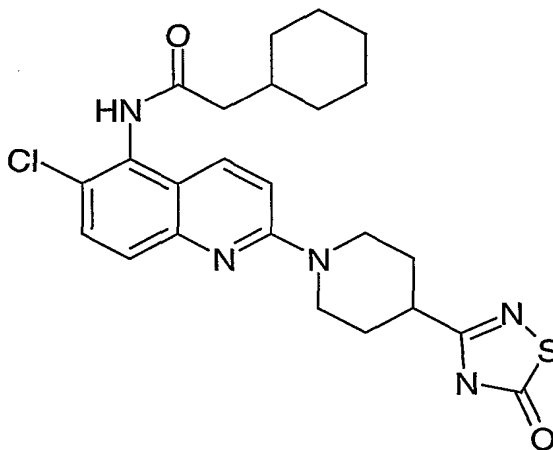
for 20 minutes. The reaction mixture was filtered and the solid was taken up in boiling methanol (20 mL) and purified by Varian NH₂ cartridge (methanol (50 mL) and then acetic acid:methanol 10:90 as eluant) to afford the title product (0.042 g).

- 5 ¹H NMR (400 MHz, d₆-DMSO) δ 9.79 (s, 1H), 7.86 (1H, d), 7.58 (1H, d), 7.50 (1H, d), 7.36 (1H, d), 4.55 (2H, d), 3.12 (2H, t), 3.00-2.91 (1H, m), 2.33 (2H, d), 1.95 (2H, d), 1.81 (3H, d), 1.75-1.57 (5H, m), 1.32-1.13 (3H, m), 1.12-0.97 (2H, m).
MS: APCI(+ve) 470.2 (M+H⁺).
m.p. 233-235 °C

10

Example 103

***N*-[6-Chloro-2-[4-(4,5-dihydro-5-oxo-1,2,4-thiadiazol-3-yl)-1-piperidinyl]-5-quinoliny]-cyclohexaneacetamide**



15

To a stirred solution of *N*-[2-[4-[amino(hydroxyimino)methyl]-1-piperidinyl]-6-chloro-5-quinoliny]-cyclohexaneacetamide (Example 102(a)) (0.1 g) in tetrahydrofuran (2 mL) was added 1,1'-thiocarbonyldiimidazole (0.042 g). After stirring for 1 hour, silica (1 g) in chloroform: methanol (5:1) (12 mL) was added and the mixture was stirred for a further 12
20 hours. The solvent was removed under vacuum, the resulting solid was taken up in methanol (20 mL) and was purified by Varian NH₂ cartridge (methanol (50 mL) and then acetic acid:methanol 10:90 as eluant) to afford the title product (0.041 g).

175

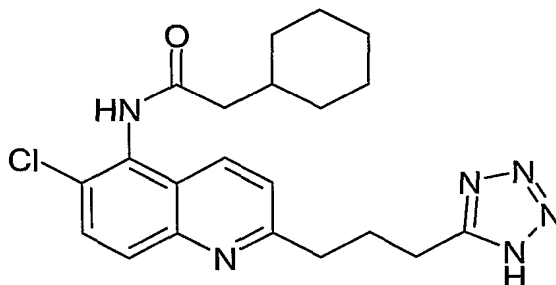
¹H NMR (400 MHz, d₆-DMSO) δ 9.79 (1H, s), 7.86 (1H, d), 7.58 (1H, d), 7.49 (1H, d), 7.35 (1H, d), 4.57 (2H, d), 3.06 (2H, t), 2.96-2.86 (1H, m), 2.33 (2H, d), 2.02-1.94 (2H, m), 1.88-1.77 (3H, m), 1.75-1.60 (5H, m), 1.32-1.11 (3H, m), 1.11-0.99 (2H, m).

MS: APCI(+ve) 486.2 (M+H⁺).

5 m.p. 275 °C

Example 104

***N*-[6-Chloro-2-[3-(1*H*-tetrazol-5-yl)propyl]-5-quinoliny]-cyclohexaneacetamide, trifluoroacetate**



10

To a stirred solution of *N*-[6-chloro-2-(3-cyanopropyl)-5-quinoliny]-cyclohexaneacetamide (prepared as in example 67 (a)) (100 mg) in toluene (2 mL) was added trimethylsilyl azide (0.07 mL) and dibutyltin oxide (6 mg). The mixture was heated to 100°C for 6 hours then allowed to cool and evaporated. Purification (HPLC, Symmetry - 0.1% aqueous trifluoroacetic acid / acetonitrile) gave the title compound as a solid (35 mg).

15

¹H NMR (400 MHz, d₆-DMSO) δ 10.00 (1H, s), 8.19 (1H, d), 7.93 (1H, d), 7.85 (1H, d), 7.59 (1H, d), 3.09-2.94 (4H, m), 2.37 (2H, d), 2.23 (2H, quintet), 1.91-1.59 (6H, m), 1.35-0.99 (5H, m).

20

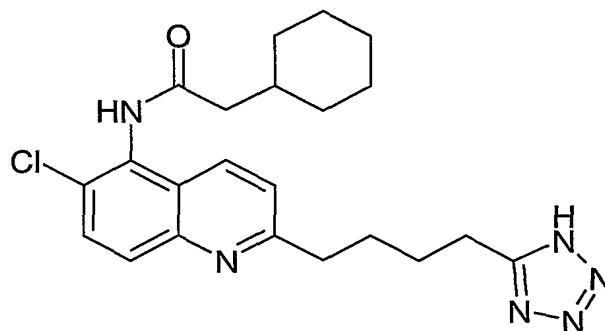
MS: APCI(+ve) 413.1/415.1 (M+H⁺).

m.p. 140-145 °C.

Example 105

25 ***N*-[6-Chloro-2-[4-(1*H*-tetrazol-5-yl)butyl]-5-quinoliny]-cyclohexaneacetamide**

176



Prepared according to the method of example 104, using *N*-[6-chloro-2-(4-cyanobutyl)-5-quinolinyl]-cyclohexaneacetamide (prepared as in example 70 (a)) (300 mg). Purification
 5 by HPLC (Symmetry - 0.1% aqueous ammonium acetate / acetonitrile) gave the title compound as a solid (70 mg).

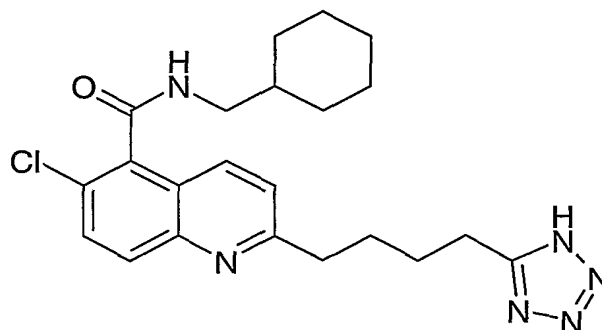
¹H NMR (400 MHz, d₆-DMSO) δ 9.96 (1H, s), 8.11 (1H, d), 7.89 (1H, d), 7.80 (1H, d),
 7.52 (1H, d), 3.01-2.86 (4H, m), 2.36 (2H, d), 1.93-1.58 (10H, m), 1.34-0.98 (5H, m).

10 MS: APCI(+ve) 427.1/429.1 (M+H⁺).

m.p. 192-195 °C.

Example 106

6-Chloro-*N*-(cyclohexylmethyl)-2-[4-(1*H*-tetrazol-5-yl)butyl]-5-quinolinecarboxamide



15

a) 6-Chloro-2-(4-cyanobutyl)-*N*-(cyclohexylmethyl)-5-quinolinecarboxamide

Prepared according to the method of example 67 (a) using 2,6-dichloro-*N*-(cyclohexylmethyl)-5-quinolinecarboxamide (prepared as in Example 43 (a)) (500 mg) and
 20 bromo(4-cyanobutyl)-zinc (30 mL, 0.5 M solution in tetrahydrofuran). Purification (SiO₂,

methanol:dichloromethane 1:200 as eluant) gave the sub-title compound as a solid (600 mg).

MS: APCI(+ve) 384.5/386.5 ($M+H^+$).

5

b) 6-Chloro-*N*-(cyclohexylmethyl)-2-[4-(1*H*-tetrazol-5-yl)butyl]-5-quinolinecarboxamide

Prepared according to the method of example 104, using 6-chloro-2-(4-cyanobutyl)-*N*-(cyclohexylmethyl)-5-quinolinecarboxamide (Example 106 (a)) (300 mg). Purification
10 (Varian NH₂ cartridge using methanol (100 mL) and then 10 % acetic acid in methanol (100 mL) as eluant) and further purification (SiO₂, methanol:dichloromethane 5:95 as eluant) gave the title compound as a solid (80 mg).

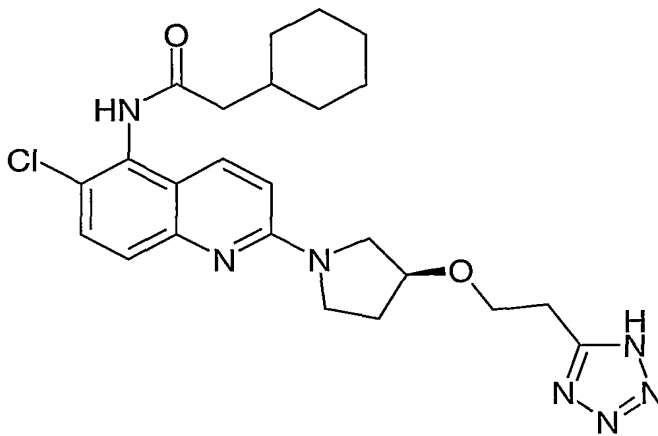
¹H NMR (300 MHz, d₆-DMSO) δ 8.71 (1H, t), 8.04 - 7.90 (2H, m), 7.75 (1H, d), 7.56 (1H,
15 d), 3.20 (2H, t), 3.03-2.86 (4H, m), 1.90-1.49 (10H, m), 1.33-0.88 (5H, m).

MS: APCI(+ve) 427.1/429.1 ($M+H^+$).

m.p. 90-93 °C.

Example 107

20 ***N*-[6-Chloro-2-[(3*S*)-3-[2-(1*H*-tetrazol-5-yl)ethoxy]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide**



a) (3S)-3-(2-Cyanoethoxy)-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester

Sodium methoxide (1.2 g) was carefully added portionwise to a stirred mixture of (3S)-3-hydroxy-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester (prepared according to the method of Bioorganic and Medicinal Chemistry Letters 2003, **13**, 3317) (2 g) and acrylonitrile (5 mL) at 0°C under nitrogen. The reaction mixture was stirred at room temperature for 15 hours and then poured into water (50 mL). The mixture was extracted with dichloromethane (2x50 mL) and the combined extracts were washed with water (50 mL) before being dried, filtered and evaporated. Purification (SiO₂, methanol:dichloromethane 2:98 as eluant) gave the sub-title compound as a colourless oil (1 g).

¹H NMR (400 MHz, d₆-DMSO) δ 4.10 (1H, s), 3.70-3.51 (2H, m), 3.39-3.15 (4H, m), 2.77-2.69 (2H, m), 1.96-1.83 (2H, m), 1.42 (9H, s).

b) 3-[(3S)-3-Pyrrolidinyloxy]-propanenitrile

To a stirred solution of (3S)-3-(2-cyanoethoxy)-1-pyrrolidinecarboxylic acid, 1,1-dimethylethyl ester (Example 107(a)) (1 g) in dichloromethane (10 mL) was added trifluoroacetic acid (3 mL). The mixture was stirred at room temperature for 30 minutes and then concentrated. Purification (Varian SCX cartridge, using methanol and then 10% ammonia in methanol as eluant) gave the sub-title compound (350 mg).

¹H NMR (400 MHz, d₆-DMSO) δ 4.04 - 3.94 (1H, m), 3.58 - 3.45 (2H, m), 2.84 - 2.59 (6H, m), 1.82 - 1.54 (2H, m), 1.23 (1H, s).

c) N-[6-Chloro-2-[(3S)-3-(2-cyanoethoxy)-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide

Prepared according to the method of example 30, using N-(2,6-dichloro-5-quinolinyl)-cyclohexaneacetamide (prepared as in Example 1(a)) (400 mg) and 3-[(3S)-3-pyrrolidinyloxy]-propanenitrile (Example 107 (b)) (350 mg). The resulting precipitate was collected by filtration and washed with acetonitrile to give the sub-title compound as a solid (370 mg).

¹H NMR (400 MHz, d₆-DMSO) δ 9.77 (1H, s), 7.85 (1H, d), 7.55 (1H, d), 7.48 (1H, d), 6.97 (1H, d), 4.30 (1H, s), 3.75-3.45 (6H, m), 2.76 (2H, t), 2.32 (2H, d), 2.18-2.04 (2H, m), 1.90-1.59 (6H, m), 1.34-0.96 (5H, m).

5 **d) *N*-[6-Chloro-2-[(3*S*)-3-[2-(1*H*-tetrazol-5-yl)ethoxy]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide**

Prepared according to the method of example 104, using *N*-[6-chloro-2-[(3*S*)-3-(2-cyanoethoxy)-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide (Example 101 (c)) (200 mg). Purification by Varian NH₂ cartridge (methanol and then 10 % acetic acid in
10 methanol as eluant) and then by Varian SCX cartridge (methanol and 10% ammonia in methanol) gave the title compound as a solid (110 mg).

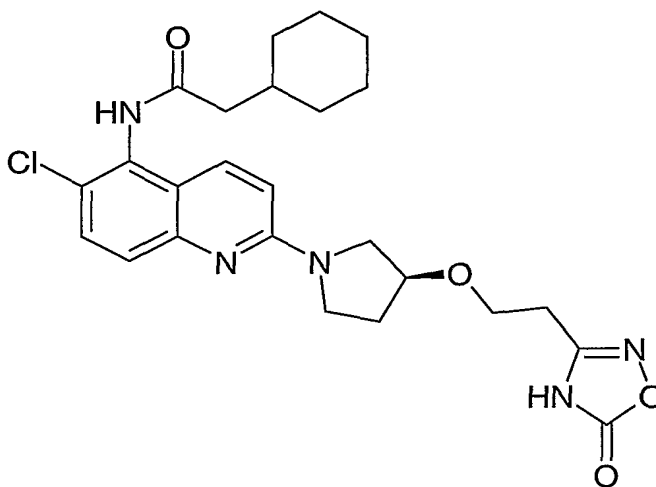
¹H NMR (400 MHz, d₆-DMSO) δ 9.77 (1H, s), 7.84 (1H, d), 7.55 (1H, d), 7.47 (1H, d), 6.93 (1H, d), 4.25 (1H, s), 3.87-3.74 (2H, m), 3.68-3.52 (3H, m), 3.49-3.36 (1H, m), 3.07
15 (2H, t), 2.32 (2H, d), 2.05 (2H, s), 1.92-1.58 (6H, m), 1.34-0.96 (5H, m).

MS: APCI(+ve) 484.2/486.2 (M+H⁺).

m.p. 177-181 °C.

Example 108

20 ***N*-[6-Chloro-2-[(3*S*)-3-[2-(4,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)ethoxy]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide**



a) *N*-[2-[(3*S*)-3-[[3-amino-3-(hydroxyimino)propyl]oxy]-1-pyrrolidinyl]-6-chloro-5-quinolinyl]-cyclohexaneacetamide

Prepared according to the method of example 102 (a) using *N*-[6-chloro-2-[(3*S*)-3-(2-cyanoethoxy)-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide (prepared as in

5 Example 107 (c)) (200 mg). The reaction mixture was concentrated and water was added to the residue. Filtration of the resulting suspension gave the sub-title compound as a solid (200 mg).

¹H NMR (300 MHz, d₆-DMSO) δ 9.76 (1H, s), 8.77 (1H, s), 7.84 (1H, d), 7.55 (1H, d),
10 7.48 (1H, d), 6.96 (1H, d), 5.34 (2H, s), 4.23 (1H, s), 3.77-3.43 (6H, m), 2.32 (2H, d), 2.21 (2H, t), 2.15-2.03 (2H, m), 1.90-1.58 (6H, m), 1.37-0.95 (5H, m).

b) *N*-[6-Chloro-2-[(3*S*)-3-[2-(4,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)ethoxy]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide

15 Prepared according to the method of Example 102 (b) using *N*-[2-[(3*S*)-3-[[3-amino-3-(hydroxyimino)propyl]oxy]-1-pyrrolidinyl]-6-chloro-5-quinolinyl]-cyclohexaneacetamide (Example 108 (a)) (200 mg). Purification (SiO₂, methanol:dichloromethane 2:98 as eluant) gave the title compound as a solid (20 mg).

20 ¹H NMR (300 MHz, d₆-DMSO) δ 9.63 (1H, s), 7.99 (1H, d), 7.82 (1H, d), 7.69 (1H, d), 7.11 (1H, d), 4.38 - 4.30 (1H, m), 3.86 - 3.61 (6H, m), 2.76 (2H, t), 2.34 (2H, d), 2.21 - 2.10 (2H, m), 1.96 - 1.56 (6H, m), 1.41 - 0.98 (5H, m).

MS: APCI(+ve) 500.2/502.2 (M+H⁺).

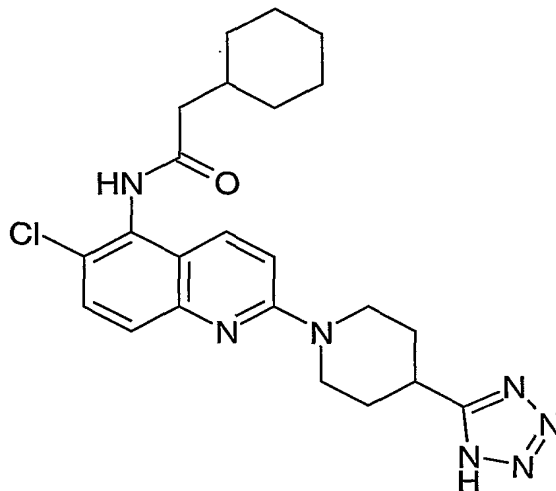
m.p. 185-190 °C.

25

Example 109

***N*-[6-Chloro-2-[4-(1*H*-tetrazol-5-yl)-1-piperidinyl]-5-quinolinyl]cyclohexaneacetamide**

181



Prepared according to the method of example 98(b), using *N*-[6-chloro-2-(4-cyano-1-piperidinyl)-5-quinoliny]-cyclohexaneacetamide (example 113) (0.07 g) to afford the title compound (0.02 g).

¹H NMR (300 MHz, CD₃OD) δ 7.83 (1H, d), 7.51-7.43 (2H, m), 7.17 (1H, d), 4.54 (2H, d), 3.27-3.02 (3H, m), 2.32 (2H, d), 2.06-1.57 (10H, m), 1.36-0.93 (5H, m).

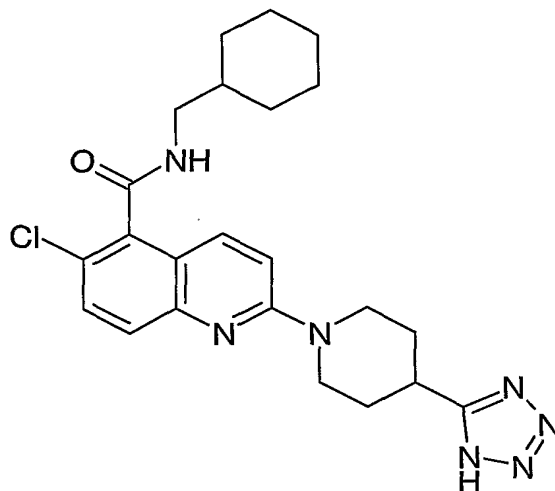
MS: APCI(+ve) 454/456 (M+H⁺).

m.p. 295-300 °C

Example 110

6-Chloro-*N*-(cyclohexylmethyl)-2-[4-(1*H*-tetrazol-5-yl)-1-piperidinyl]-5-quinolinecarboxamide

182



a) 6-Chloro-2-(4-cyano-1-piperidinyl)-N-(cyclohexylmethyl)-5-quinolinecarboxamide

Prepared according to the method of example 51, using 2,6-dichloro-*N*-

- 5 (cyclohexylmethyl)-5-quinolinecarboxamide (Example 43(a)) (0.25 g), and 4-cyanopiperidine hydrochloride (0.25 g) to afford the title compound (0.27 g).

¹H NMR (300 MHz, CD₃OD) δ 7.78 (1H, d), 7.54 (1H, d), 7.42 (1H, d), 7.17 (1H, d), 4.00 (2H, ddd), 3.51 (2H, ddd), 3.19 (2H, s), 2.99 (1H, dt), 1.99-1.89 (2H, m), 1.82-1.49 (8H, m), 1.30-1.10 (3H, m), 1.04-0.90 (2H, m).

MS: APCI(+ve) 411/413 (M+H⁺).

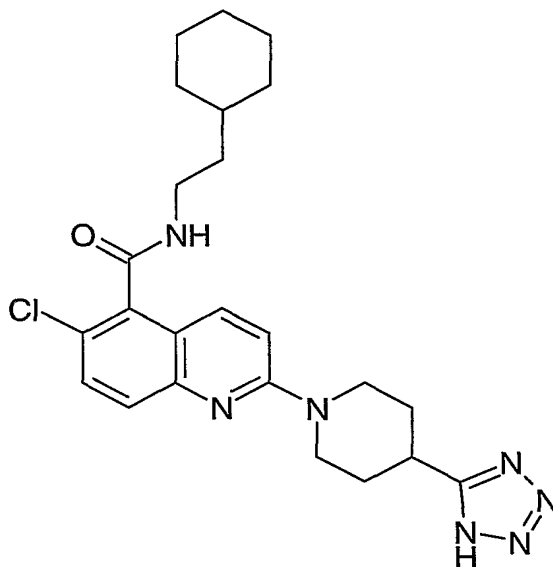
b) 6-Chloro-N-(cyclohexylmethyl)-2-[4-(1H-tetrazol-5-yl)-1-piperidinyl]-5-quinolinecarboxamide

- 15 Prepared according to the method of example 98 (b), using 6-chloro-2-(4-cyano-1-piperidinyl)-*N*-(cyclohexylmethyl)-5-quinolinecarboxamide (Example 110 (a)) (0.25 g) to afford the title compound (0.15 g).

¹H NMR (300 MHz, CD₃OD) δ 7.79 (1H, d), 7.54 (1H, d), 7.42 (1H, d), 7.21 (1H, d), 4.57 (2H, d), 3.30 (1H, tt), 3.13 (2H, t), 2.08 (2H, d), 1.79 (4H, d), 1.73-0.89 (11H, m).

MS: APCI(+ve) 454/456 (M+H⁺).

m.p. 255-257 °C

Example 111**6-Chloro-*N*-(2-cyclohexylethyl)-2-[4-(1*H*-tetrazol-5-yl)-1-piperidinyl]-5-quinolinecarboxamide**

5

a) 6-Chloro-2-(4-cyano-1-piperidinyl)-*N*-(2-cyclohexylethyl)-5-quinolinecarboxamide

Prepared according to the method of example 51, using 2,6-dichloro-*N*-(cyclohexylethyl)-5-quinolinecarboxamide (Example 94 (d)) (0.35 g), and 4-cyanopiperidine hydrochloride (0.25 g) to afford the title compound (0.12 g).

10

¹H NMR (400 MHz, d₆-DMSO) δ 8.59 (1H, t), 7.76 (1H, d), 7.57 (1H, d), 7.53 (1H, d), 7.37 (1H, d), 4.08-3.98 (2H, m), 3.53 (2H, t), 3.36 (2H, t), 3.21-3.13 (1H, m), 2.02-1.93 (2H, m), 1.81-1.58 (7H, m), 1.49-1.39 (3H, m), 1.27-1.11 (3H, m), 0.97-0.86 (2H, m). MS: APCI(+ve) 425/427 (M+H⁺).

15

b) 6-Chloro-*N*-(cyclohexylmethyl)-2-[4-(1*H*-tetrazol-5-yl)-1-piperidinyl]-5-quinolinecarboxamide

Prepared according to the method of example 98 (b), using 6-chloro-2-(4-cyano-1-piperidinyl)-*N*-(2-cyclohexylethyl)-5-quinolinecarboxamide (Example 111 (a)) (0.12 g) to afford the title compound (0.07g).

20

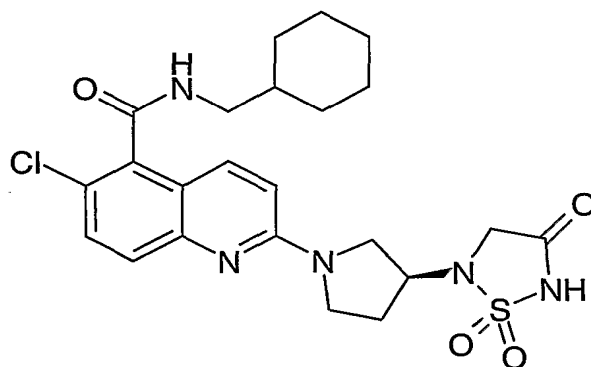
^1H NMR (400 MHz, d_6 -DMSO) δ 8.59 (1H, t), 7.77 (1H, d), 7.57 (1H, d), 7.53 (1H, d), 7.41 (1H, d), 4.57 (2H, d), 3.43-3.32 (3H, m), 3.20 (1H, t), 2.09 (2H, d), 1.79-1.59 (7H, m), 1.49-1.35 (3H, m), 1.27-1.11 (3H, m), 0.97-0.86 (2H, m).

MS: APCI(+ve) 468/470 ($\text{M}+\text{H}^+$).

5 m.p. 252-255 °C

Example 112

6-Chloro-*N*-(cyclohexylmethyl)-2-[(3*S*)-3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-1-pyrrolidinyl]-5-quinolinecarboxamide



10

a) *N*-[(3*S*)-1-[6-chloro-5-[[[(cyclohexylmethyl)amino]carbonyl]-2-quinoliny]-3-pyrrolidinyl]-glycine, ethyl ester

A stirred solution of 2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-chloro-*N*-(cyclohexylmethyl)-5-quinolinecarboxamide (prepared as in Example 44) (450 mg), ethyl chloroacetate (0.21 mL) and triethylamine (0.33 mL) in acetonitrile (3 mL) was heated at 100°C in a microwave for 1 hour after which it was cooled to room temperature and concentrated. Purification by chromatography (SiO_2 , dichloromethane: methanol: ammonia in methanol (7 M) 96:3:1 as eluant) gave the sub-title compound as a solid (490 mg).

20

MS: APCI(+ve) 473 ($\text{M}+\text{H}^+$).

b) *N*-[(3*S*)-1-[6-Chloro-5-[[[(cyclohexylmethyl)amino]carbonyl]-2-quinoliny]-3-pyrrolidinyl]-*N*-[[[(1,1-dimethylethoxy)carbonyl]amino]sulfonyl]-glycine, ethyl ester

A solution of 2-methyl-2-propanol (140 mg) in dichloromethane (2 mL) was added over 15 minutes to a stirred solution of chlorosulfonyl isocyanate (0.17 mL) in dichloromethane (16 mL) under nitrogen at 0°C. The mixture was allowed to warm to room temperature over 2 hours and was then added over 20 minutes to a stirred solution of *N*-[(3*S*)-1-[6-chloro-5-[[[(cyclohexylmethyl)amino]carbonyl]-2-quinoliny]-3-pyrrolidinyl]-glycine, ethyl ester (Example 112 (a)) (490 mg) and triethylamine (0.25 mL) in dichloromethane (10 mL) under nitrogen at 0°C. After 3 hours, deionised water (10 mL) was added, the layers were separated and the aqueous fraction was extracted with dichloromethane (2 x 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated to give an oil. Purification by chromatography (SiO₂, dichloromethane: methanol 99:1 as eluant) gave the sub-title compound as a solid (670 mg).

MS: APCI(+ve) 653/655 (M+H⁺).

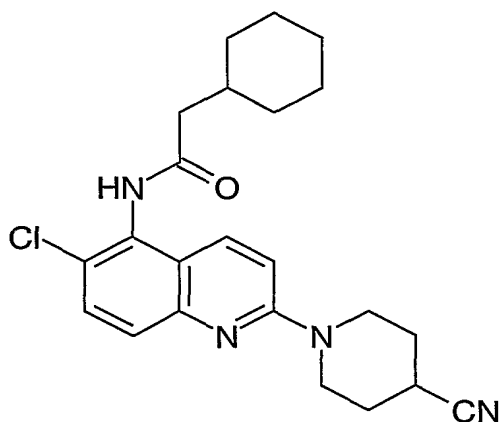
c) 6-Chloro-*N*-(cyclohexylmethyl)-2-[(3*S*)-3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-1-pyrrolidinyl]-5-quinolinecarboxamide

N-[(3*S*)-1-[6-Chloro-5-[[[(cyclohexylmethyl)amino]carbonyl]-2-quinoliny]-3-pyrrolidinyl]-*N*-[[[(1,1-dimethylethoxy)carbonyl]amino]sulfonyl]-glycine, ethyl ester (Example 112 (b)) (670 mg) was dissolved in dichloromethane (5 mL). Trifluoroacetic acid (1 mL) was added and the mixture stirred for 3 hours before being concentrated. Sodium methoxide (25% in methanol, 3 mL) was added and the mixture was stirred under nitrogen for 2 hours. The products were concentrated onto silica gel and purified by chromatography (SiO₂, dichloromethane: methanol 92:8 as eluant). Further purification by HPLC (Symmetry - 0.1% aqueous trifluoroacetic acid / acetonitrile) gave the title compound as a solid (20 mg).

¹H NMR (400 MHz, d₆-DMSO) δ 8.80 (1H, t), 8.01-7.88 (2H, m), 7.83-7.76 (1H, m), 7.36-7.27 (1H, m), 7.18-6.95 (1H, m), 3.89-3.68 (7H, m), 3.19 (2H, m), 2.38-2.22 (2H, m), 1.88-1.49 (6H, m), 1.35-1.11 (3H, m), 1.09-0.87 (2H, m).

MS: APCI(+ve) 506/508 (M+H⁺).

Example 113

***N*-[6-Chloro-2-(4-cyano-1-piperidinyl)-5-quinoliny]-cyclohexaneacetamide**

Prepared according to the method of example 51, using *N*-(2,6-dichloro-5-quinoliny)-cyclohexaneacetamide (Example 1(a)) (0.10 g), and 4-cyanopiperidine hydrochloride (0.21 g) to afford the title compound (0.08 g).

¹H NMR (300 MHz, CD₃OD) δ 7.98 (1H, d), 7.62 (2H, s), 7.28 (1H, d), 4.17-4.07 (2H, m), 3.70-3.59 (2H, m), 3.17-3.07 (1H, m), 2.44 (2H, d), 2.13-1.69 (10H, m), 1.47-1.09 (5H, m).

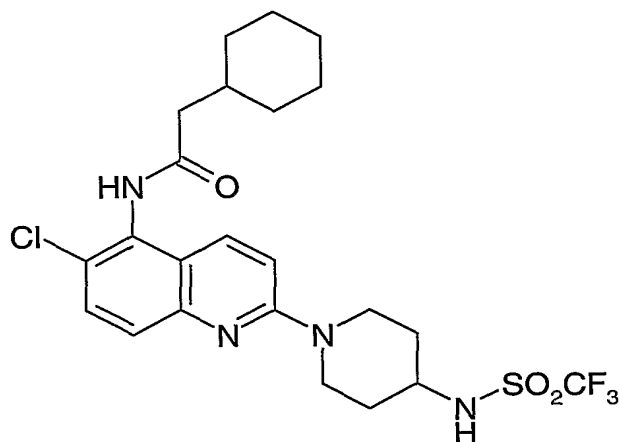
MS: APCI(+ve) 411/413 (M+H⁺).

m.p. = 235-237°C

Example 114

***N*-[6-Chloro-2-[4-[[trifluoromethyl)sulfonyl]amino]-1-piperidinyl]-5-quinoliny]-cyclohexaneacetamide**

187



To a solution of *N*-[2-(4-amino-1-piperidiny)-6-chloro-5-quinoliny]-cyclohexanecarboxamide (Example 32) (0.05 g) in dichloromethane (5 mL) cooled to -78°C and under a nitrogen atmosphere, was added triethylamine (0.10 mL) followed by triflic anhydride (0.12 mL). The mixture was allowed to warm to room temperature and then quenched by the addition of water (5 mL). Saturated sodium bicarbonate solution (5 mL) was added and the organics collected, dried and concentrated. Purification (NH_2 ion-exchange cartridge, 1% AcOH in acetonitrile as eluant), followed by trituration with diethylether gave the title compound (0.02 g).

^1H NMR (300 MHz, CD_3OD) δ 7.83 (1H, d), 7.47 (2H, s), 7.14 (1H, d), 4.45 (2H, d), 3.66-3.53 (1H, m), 3.02 (2H, t), 2.37 (2H, d), 1.97-1.44 (8H, m), 1.35-0.93 (7H, m).

MS: APCI(+ve) 533/535 ($\text{M}+\text{H}^+$).

m.p. = $187\text{-}189^{\circ}\text{C}$

Pharmacological Analysis

Certain compounds such as benzoylbenzoyl adenosine triphosphate (bbATP) are known to be agonists of the P2X_7 receptor, effecting the formation of pores in the plasma membrane (Drug Development Research (1996), 37(3), p.126). Consequently, when the receptor is

activated using bbATP in the presence of ethidium bromide (a fluorescent DNA probe), an increase in the fluorescence of intracellular DNA-bound ethidium bromide is observed. The increase in fluorescence can be used as a measure of P2X₇ receptor activation and therefore to quantify the effect of a compound on the P2X₇ receptor.

5

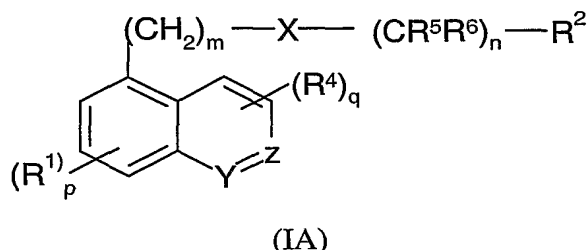
In this manner, each of the title compounds of the Examples was tested for antagonist activity at the P2X₇ receptor. Thus, the test was performed in 96-well flat bottomed microtitre plates, the wells being filled with 250 µl of test solution comprising 200 µl of a suspension of THP-1 cells (2.5×10^6 cells/ml) containing 10^{-4} M ethidium bromide, 25 µl of a high potassium buffer solution containing 10^{-5} M bbATP, and 25 µl of the high potassium buffer solution containing 3×10^{-5} M test compound. The plate was covered with a plastics sheet and incubated at 37 °C for one hour. The plate was then read in a Perkin-Elmer fluorescent plate reader, excitation 520 nm, emission 595 nm, slit widths: Ex 15 nm, Em 20 nm. For the purposes of comparison, bbATP (a P2X₇ receptor agonist) and pyridoxal 5-phosphate (a P2X₇ receptor antagonist) were used separately in the test as controls. From the readings obtained, a pIC₅₀ figure was calculated for each test compound, this figure being the negative logarithm of the concentration of test compound necessary to reduce the bbATP agonist activity by 50%. Each of the compounds of the Examples demonstrated antagonist activity, having a pIC₅₀ figure > 5.5. For example, the following table shows the pIC₅₀ figures for a representative selection of compounds:

10
15
20

Compound of Example No.	pIC ₅₀
5	6.9
17	7.6
20	6.9
28	7.4
33	7.6
37	7.3
42	6.5
73	6.4
102	6.7
112	6.5
24	6.3

CLAIMS

- 5 1. A compound of formula (IA)



or a pharmaceutically acceptable salt, prodrug or solvate thereof,

10 wherein

p is 0, 1 or 2;

each R¹ independently represents halogen or C₁-₆ alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C₁-₆ alkoxy;

q is 0, 1 or 2;

15 each R⁴ independently represents halogen or C₁-₆ alkyl optionally substituted by at least one substituent selected from hydroxyl, halogen and C₁-₆ alkoxy;

m is 0, 1, 2 or 3;

X is -C(O)NH- or -NHC(O)-;

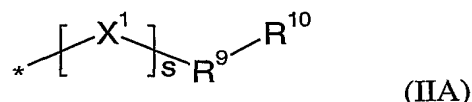
n is 0, 1, 2 or 3;

20

within each grouping CR⁵R⁶, R⁵ and R⁶ each independently represent hydrogen, C₁-₆ alkyl or R⁵ and R⁶ together with the carbon atom to which they are both attached can form a 3- to 6- membered cycloalkyl ring;

25 R² represents a 4- to 9-membered cycloalkyl ring system, which cycloalkyl ring system can be optionally substituted by at least one substituent independently selected from halogen, hydroxyl, -S(O)ₑ C₁-₆alkyl, -NR⁷R⁸, -C(O)OR¹², -OC(O)R¹³, -C(O)NR¹⁴R¹⁵, -SO₂NR¹⁶ R¹⁷, -NR¹⁸SO₂R¹⁹, C₁-₆ alkoxy, C₁-₆ hydroxyalkyl or a C₁-₆ alkyl group which C₁-₆ alkyl group can be optionally substituted by at least one halogen; f is 0, 1 or 2;

one of Y or Z is nitrogen and the other is a group CR³ wherein R³ is a group of formula (IIA)



- 5 wherein X¹ represents an oxygen or sulphur atom, or a group >N-R¹¹ wherein R¹¹ is hydrogen or a C₁₋₅ alkyl group which can be optionally substituted by one or more substituents selected from hydroxyl, halogen or C₁₋₆alkoxy; s is 0 or 1;

- 10 R⁹ represents a bond or a C₁₋₅ alkylene group, which can be optionally substituted by at least one substituent selected from hydroxyl, halogen and C₁-C₆ alkoxy;

R¹⁰ represents hydrogen, hydroxyl, carboxyl, -C(O)OR²⁰, -NR²¹R²², -C(O)NOH, or a group -WR²³;

- 15 or R¹⁰ represents a 4- to 9-membered carbocyclic or heterocyclic ring, either of which may include bridging groups, which carbocyclic and heterocyclic ring can be optionally substituted by at least one substituent selected from halogen, hydroxyl, =O, carboxyl, cyano, C₁-C₆ alkyl, C₁-C₆ hydroxyalkyl, a group -W'R²⁴, -C(O)NOH, -(CH₂)_tNR²⁵R²⁶, -(CH₂)_tC(O)NR²⁷R²⁸, -(CH₂)_tR²⁹-(CH₂)_tNR³⁰C(O)R³¹, -S(O)_rR³², NR³³SO₂R³⁴,
 20 NR³⁵C(O)NR³⁶S(O)_rR³⁷, -S(O)_r(CH₂)_tNR³⁸R³⁹, -NR⁴⁰S(O)_rNR⁴¹R⁴², -S(O)_r(CH₂)_tC(O)OR⁴³, or -M(CH₂)_tC(O)OR⁴⁴ wherein M represents a bond, O, or a group >NR⁴⁵;

t is 0, 1, 2, 3, 4, 5 or 6;

- 25 r is 0, 1 or 2;

- R²¹ and R²² are independently selected from hydrogen, C₂₋₇ alkenyl, C₁₋₆ alkylcarbonyl, -SO₂R⁴⁶, -C(O)NHSO₂R⁴⁷, a 3- to 8-membered carbocyclic or heterocyclic ring which carbocyclic or heterocyclic ring can be optionally substituted by at least one substituent
 30 selected from halogen, hydroxyl and carboxyl,

or R^{21} and R^{22} may independently represent a C_{1-7} alkyl group which C_{1-7} alkyl group can be optionally substituted by at least one substituent independently selected from halogen, carboxyl, hydroxyl, $-NH(CH_2)_{2-4}OH$, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxy carbonyl, $-NR^{48}R^{49}$, $-C(O)NR^{50}R^{51}$, $-NR^{52}C(O)R^{53}$, $-NR^{54}SO_2R^{55}$ and $-NR^{67}C(O)NR^{68}SO_2R^{56}$;

5

W and W' independently represent a bond, O, $S(O)_p$, $-NR^{57}C(O)-$, $-C(O)NR^{58}-$, $-SO_2NR^{59}$, $-NR^{60}SO_2-$, $>NR^{61}$, C_{1-6} alkylene, or a group $-O(CH_2)_{1-6}-$, $-S(O)_p(CH_2)_{1-6}-$, $-NR^{62}(CH_2)_{1-6}-$, $-(CH_2)_{1-3}O(CH_2)_{1-3}-$, $-(CH_2)_{1-3}S(O)_p(CH_2)_{1-3}-$, $-(CH_2)_{1-3}NR^{63}(CH_2)_{1-3}-$, $-(CH_2)_{1-3}NR^{64}C(O)(CH_2)_{0-3}-$, $-(CH_2)_{1-3}C(O)NR^{65}(CH_2)_{0-3}-$, or $-S(O)_p(CH_2)_{1-6}NR^{66}-$; p is 0, 1 or 2;

10

R^{23} and R^{24} independently represent a 3- to 10-membered carbocyclic or heterocyclic ring comprising from 1 to 5 heteroatoms independently selected from nitrogen, oxygen and sulphur, which carbocyclic or heterocyclic ring can be optionally substituted with at least one substituent selected from hydroxyl, $=O$, $=S$, nitro, cyano, amino, halogen $-SO_2C_{1-6}$ alkyl, C_{1-6} alkyl carbonyl, C_{1-6} alkoxy carbonyl, C_{1-6} alkyl amino, di- C_{1-6} alkyl amino, and a C_{1-6} alkyl group which C_{1-6} alkyl group can be optionally substituted by at least one substituent selected from halogen and hydroxyl;

15

20

R^7 , R^8 , R^{12} , R^{13} , R^{14} , R^{15} , R^{16} , R^{17} , R^{18} and R^{19} each independently represent a hydrogen atom or C_{1-6} alkyl group optionally substituted by at least one substituent selected from hydroxyl, halogen and C_{1-6} alkoxy, or any of R^7 and R^8 , R^{14} and R^{15} , R^{16} and R^{17} together with the nitrogen atom to which they are both attached can form a 3- to 8-membered saturated heterocyclic ring;

25

R^{20} , R^{34} , R^{37} , R^{46} , R^{47} , R^{54} , R^{55} , R^{56} , R^{57} , R^{58} , R^{59} , R^{60} , R^{61} , R^{62} , R^{63} , R^{64} , R^{65} , R^{66} , R^{67} and R^{68} each independently represent hydrogen or a C_{1-6} alkyl group which can be optionally substituted by at least one substituent selected from halogen and hydroxyl;

30

R^{25} , R^{26} , R^{27} , R^{28} , R^{30} , R^{31} , R^{32} , R^{33} , R^{35} , R^{36} , R^{38} , R^{39} , R^{40} , R^{41} , R^{42} , R^{43} , R^{44} , R^{45} , R^{48} , R^{49} , R^{50} , R^{51} , R^{52} and R^{53} each independently represent a hydrogen atom or a C_{1-6} alkyl, C_{2-6} hydroxyalkyl or a C_{3-8} cycloalkyl group, or any of R^{25} and R^{26} , R^{27} and R^{28} , R^{38} and

R^{39} , R^{41} and R^{42} , R^{48} and R^{49} , R^{50} and R^{51} together with the nitrogen atom to which they are both attached can form a 3- to 8-membered saturated heterocyclic ring; and R^{29} is aryl.

2. A compound according to claim 1 wherein Y is nitrogen and Z is a group CR_3 .

3. A compound according to claim 1 or claim 2, wherein n is 1 or 2.

4. A compound according to any one of claims 1 to 3, wherein R^2 represents a cyclopentyl or cyclohexyl ring optionally substituted with a C_{1-4} alkyl group.

5. A compound according to any one of claims 1 to 4, wherein in formula (IIA) s is 0; R^9 represents a bond; and R^{10} represents an optionally substituted 4- to 9-membered carbocyclic or heterocyclic ring.

6. A compound according to claim 5, wherein in formula (IIA) s is 0; R^9 represents a bond; and R^{10} represents a pyrrolidinyl, piperidinyl, piperazinyl or homopiperidinyl group, which can be optionally substituted by at least one substituent selected from hydroxyl, cyano, carboxyl, methyl, $-NH_2$, $-NHCH_3$, $-NHCH_2CH_2OH$, $-CH_2C(O)OH$, $-NHCH_2C(O)OH$, $-NHCH_2CH_2C(O)OH$, $-CH_2NHCH_3$, $-CH_2NHCH_2CH_2OH$, $-SO_2CH_2CH_2OH$, $-N(CH_2CH_2OH)C(O)OC(CH_3)_3$, $-NH-SO_2CF_3$, $-NHC(O)NHSO_2CH_3$.

7. A compound according to any one of claims 1 to 3, wherein in formula (IIA) R^9 represents a C_{1-5} alkylene group which can be optionally substituted by at least one hydroxyl; and R^{10} represents hydrogen, hydroxyl, carboxyl, $-C(O)OR^{20}$, $-NR^{21}R^{22}$, $-C(O)NOH$, or a group $-WR^{23}$.

8. A compound according to any one of claims 1 to 3, wherein R^{10} represents $-WR^{23}$ or R^{10} represents a 4- to 9-membered carbocyclic or heterocyclic ring, either of which may include bridging groups, which carbocyclic and heterocyclic ring is substituted by at least one substituent $-W'R^{24}$.

9. A compound of formula (IA), or pharmaceutically acceptable salt, prodrug or solvate thereof, according to claim 1 being:

N-[6-Chloro-2-(4-piperidinylmethyl)-5-quinolinyl]-cyclohexaneacetamide, dihydrochloride,

5 *N*-[6-Chloro-2-(1-piperazinyl)-5-quinolinyl]-cyclohexaneacetamide, dihydrochloride,

N-[6-Chloro-2-[methyl[3-(methylamino)propyl]amino]-5-quinolinyl]-cyclohexaneacetamide, dihydrochloride,

6-Chloro-*N*-(cyclohexylmethyl)-2-methyl-5-quinolinecarboxamide, hydrochloride,

10 *N*-[6-Chloro-2-[(3-hydroxypropyl)amino]-5-quinolinyl]-cyclohexaneacetamide, hydrochloride,

N-[6-Chloro-2-[(2*R*)-2,3-dihydroxypropyl]amino]-5-quinolinyl]-cyclohexaneacetamide,

4-[[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]amino]-butanoic acid,

15 *N*-[6-Chloro-2-[methyl[3-(methylamino)propyl]amino]-5-quinolinyl]-4-(trifluoromethyl)-cyclohexaneacetamide, dihydrochloride,

N-[6-Chloro-2-(1-piperazinyl)-5-quinolinyl]-4-(trifluoromethyl)-cyclohexaneacetamide,

20 *N*-[6-Chloro-2-(hexahydro-1*H*-1,4-diazepin-1-yl)-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-[(*cis*-3,5-dimethyl-1-piperazinyl)-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-(4-methyl-1-piperazinyl)-5-quinolinyl]-cyclohexaneacetamide, dihydrochloride,

25 *N*-[6-Chloro-2-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl]-5-quinolinyl]-cyclohexaneacetamide, acetate,

N-[6-Chloro-2-[(3*R*)-3-pyrrolidinylamino]-5-quinolinyl]-cyclohexaneacetamide, dihydrochloride,

30 *N*-[2-[3-(Ethylamino)propyl]-6-methyl-5-quinolinyl]-cyclohexaneacetamide, dihydrochloride,

N-[6-Chloro-2-[3-(ethylamino)propyl]-5-quinolinyl]-cyclohexaneacetamide, dihydrochloride,

- N*-[6-Chloro-2-[[2-[(2-hydroxyethyl)amino]ethyl]amino]-5-quinolinyl]-cyclohexaneacetamide, dihydrochloride,
- N*-5-Quinoliny-cyclohexaneacetamide,
- 1-Methyl-*N*-5-quinoliny-cyclohexaneacetamide,
- 5 4-Methyl-*N*-5-quinoliny-cyclohexaneacetamide,
- N*-5-Quinoliny-cyclopentanepropanamide,
- N*-[6-Chloro-2-[3-[(3-hydroxypropyl)amino]propyl]-5-quinolinyl]-cyclohexaneacetamide,
- N*-[2-(3-Aminopropyl)-6-chloro-5-quinolinyl]-cyclohexaneacetamide,
- 10 *N*-[6-Chloro-2-[3-[[[(methylsulfonyl)amino]carbonyl]amino]propyl]-5-quinolinyl]-cyclohexaneacetamide,
- N*-[2-[3-(Butylamino)propyl]-6-chloro-5-quinolinyl]-cyclohexaneacetamide dihydrochloride,
- N*-[6-Chloro-2-[methyl[3-(methylamino)propyl]amino]-5-quinolinyl]-1-cyclohexyl-
- 15 cyclopropanecarboxamide, hydrochloride,
- N*-[6-Chloro-2-(1-piperaziny)-5-quinolinyl]-1-cyclohexyl-cyclopropanecarboxamide,
- N*-[6-Chloro-2-[(3*R*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,
- 20 *N*-[6-Chloro-2-[(3*S*)-3-hydroxy-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,
- N*-[2-[(3*R*)-3-Amino-1-pyrrolidinyl]-6-chloro-5-quinolinyl]-cyclohexaneacetamide,
- N*-[2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-chloro-5-quinolinyl]-cyclohexaneacetamide,
- N*-[2-(4-Amino-1-piperidinyl)-6-chloro-5-quinolinyl]-cyclohexaneacetamide,
- 25 *N*-[6-Chloro-2-[(3*R*)-3-(methylamino)-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,
- N*-[6-Chloro-2-[(3*R*)-3-[(2-hydroxyethyl)amino]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,
- N*-[6-Chloro-2-[(3*S*)-3-(methylamino)-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,
- 30 cyclohexaneacetamide,
- N*-[6-Chloro-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-[(3*R*)-3-hydroxy-1-piperidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-methyl-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Methyl-2-(1-piperazinyl)-5-quinolinyl]-cyclohexaneacetamide,

5 *N*-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-glycine,

N-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]- β -alanine,

6-Chloro-*N*-(cyclohexylmethyl)quinoline-5-carboxamide,

6-Chloro-*N*-(cyclohexylmethyl)-2-(1-piperazinyl)-5-quinolinecarboxamide, dihydrochloride,

10 2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-chloro-*N*-(cyclohexylmethyl)-5-quinolinecarboxamide,

6-Chloro-*N*-(cyclohexylmethyl)-2-[methyl[3-(methylamino)propyl]amino]-5-quinoline carboxamide, dihydrochloride,

15 6-Chloro-*N*-(cyclohexylmethyl)-2-[methyl[2-(methylamino)ethyl]amino]-5-quinolinecarboxamide, dihydrochloride,

6-Chloro-*N*-(cyclohexylmethyl)-2-[3-[(3-hydroxypropyl)amino]propyl]-5-quinolinecarboxamide,

2-[(3*R*)-3-Amino-1-pyrrolidinyl]-6-chloro-*N*-(cyclohexylmethyl)-5-quinolinecarboxamide, dihydrochloride,

20 *N*-(2-Amino-6-chloro-5-quinolinyl)-cyclohexaneacetamide, trifluoroacetate,

6-Chloro-*N*-(cyclohexylmethyl)-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-pyrrolidinyl]-5-quinolinecarboxamide, hydrochloride,

2-[(3*S*)-3-Amino-1-piperidinyl]-6-chloro-*N*-(cyclohexylmethyl)-5-quinolinecarboxamide,

25 6-Chloro-*N*-(cyclohexylmethyl)-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-piperidinyl]-5-quinolinecarboxamide, hydrochloride,

6-Chloro-*N*-(cyclohexylmethyl)-2-(3-hydroxy-1-azetidiny)-5-quinolinecarboxamide,

2-[(3*S*)-3-Amino-1-pyrrolidinyl]-*N*-(cyclohexylmethyl)-5-quinolinecarboxamide,

30 6-Chloro-*N*-(cyclohexylmethyl)-2-[3-[(2-hydroxyethyl)amino]-1-azetidiny]-5-quinolinecarboxamide,

[1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-3-pyrrolidinyl](2-hydroxyethyl)-carbamic acid 1,1-dimethylethyl ester,

N-(Cyclohexylmethyl)-6-methyl-5-quinolinecarboxamide,

2-[(3*S*)-3-Amino-1-pyrrolidinyl]-*N*-(cyclohexylmethyl)-6-methyl-5-

5 quinolinecarboxamide, acetate,

N-[2-[(3*S*)-3-Amino-1-pyrrolidinyl]methyl]-6-chloro-5-quinolinyl]-cyclohexaneacetamide,

N-[2-[(3*S*)-3-Amino-1-piperidinyl]-6-chloro-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-piperidinyl]-5-quinolinyl]-

10 cyclohexaneacetamide,

N-[2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-chloro-5-quinolinyl]-cyclopentanepropanamide,

N-[6-Chloro-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-pyrrolidinyl]-5-quinolinyl]-cyclopentanepropanamide,

15 *N*-[6-Chloro-2-[4-(1,5-dihydro-5-oxo-4*H*-1,2,4-triazol-4-yl)-1-piperidinyl]-5-quinolinyl]-cyclohexaneacetamide,

1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-*D*-proline, trifluoroacetate,

1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-4-piperidinecarboxylic acid, lithium salt,

20 6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinebutanoic acid,

1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-4-piperidineacetic acid,

4-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinyl]-1-piperazineacetic acid, lithium salt,

6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinolinepentanoic acid, 1-[6-Chloro-5-

25 [[(cyclohexylmethyl)amino]carbonyl]-2-quinolinyl]-*D*-proline,

1-[6-Chloro-5-[[[(cyclohexylmethyl)amino]carbonyl]-2-quinolinyl]-*L*-proline, trifluoroacetate,

4-[6-Chloro-5-[[[(cyclohexylmethyl)amino]carbonyl]-2-quinolinyl]-1-piperazineacetic acid, acetate,

30 1-[6-Chloro-5-[[[(cyclohexylmethyl)amino]carbonyl]-2-quinolinyl]-4-piperidinecarboxylic acid, sodium salt,

1-[6-Chloro-5-[[cyclohexylmethyl]amino]carbonyl]-2-quinoliny]-4-piperidineacetic acid, trifluoroacetate,

1-[6-Chloro-5-[(2-cyclohexylethyl)amino]carbonyl]-2-quinoliny]-4-piperidinecarboxylic acid,

5 1-[6-Chloro-5-[(3-cyclopentyl-1-oxopropyl)amino]-2-quinoliny]-4-piperidinecarboxylic acid,

1-[6-Chloro-5-[(3-cyclohexyl-1-oxopropyl)amino]-2-quinoliny]-4-piperidinecarboxylic acid, potassium salt,

10 1-[6-Chloro-5-[(1-methylcyclohexyl)acetyl]amino]-2-quinoliny]-4-piperidinecarboxylic acid,

N-[6-Chloro-2-[3-[(2-hydroxyethyl)amino]-1-piperidinyl]-5-quinoliny]-cyclohexaneacetamide,

N-[6-Chloro-2-[2-[(2-hydroxyethyl)amino]methyl]-1-pyrrolidinyl]-5-quinoliny]-cyclohexaneacetamide,

15 *N*-[6-Chloro-2-[3-(methylamino)-1-piperidinyl]-5-quinoliny]-cyclohexaneacetamide,

N-[6-Chloro-2-[2-[(methylamino)methyl]-1-pyrrolidinyl]-5-quinoliny]-cyclohexaneacetamide,

20 *N*-[2-[(3*R*)-3-Hydroxy-1-pyrrolidinyl]-6-methyl-5-quinoliny]-cyclohexaneacetamide,

N-[(3*S*)-1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinoliny]-3-pyrrolidinyl]-glycine,

N-[2-[(3*S*)-3-[(2-Hydroxyethyl)amino]-1-pyrrolidinyl]-6-methyl-5-quinoliny]-cyclohexaneacetamide,

25 *N*-[(3*S*)-1-[6-Chloro-5-[(cyclohexylacetyl)amino]-2-quinoliny]-3-pyrrolidinyl]- β -alanine,

N-[6-Chloro-2-[(3*S*)-3-[[trifluoromethyl]sulfonyl]amino]-1-pyrrolidinyl]-5-quinoliny]-cyclohexaneacetamide,

30 *N*-[6-Chloro-2-[(3*S*)-3-[[[(methylsulfonyl)amino]carbonyl]amino]-1-pyrrolidinyl]-5-quinoliny]-cyclohexaneacetamide,

N-[2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-chloro-5-quinoliny]-cyclohexanepropanamide,

N-[6-Chloro-2-[methyl[3-(methylamino)propyl]amino]-5-quinolinyl]-cyclohexanepropanamide,

N-[6-Chloro-2-(1-piperazinyl)-5-quinolinyl]-cyclohexanepropanamide,

N-[6-Chloro-2-[(3*S*)-3-[(2-hydroxyethyl)amino]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexanepropanamide,

2-[(3*S*)-3-Amino-1-pyrrolidinyl]-6-chloro-*N*-(2-cyclohexylethyl)-5-quinolinecarboxamide, ditrifluoroacetate,

N-[6-Chloro-2-[(3*S*)-3-[(2-hydroxyethyl)sulfonyl]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,

10 *N*-[6-Chloro-2-[(3*S*)-3-cyano-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[1-[6-Chloro-5-[(cyclohexylmethyl)amino]carbonyl]-2-quinolinyl]-3-azetidiny]- β -alanine,

6-Chloro-*N*-(cyclohexylmethyl)-2-[3-(1*H*-tetrazol-5-yl)-1-azetidiny]-5-quinolinecarboxamide,

15 *N*-[6-Chloro-2-[(3*S*)-3-(1*H*-tetrazol-5-yl)-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-[(3*R*)-3-(1*H*-tetrazol-5-yl)-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,

20 *N*-[6-Chloro-2-[(3*S*)-3-[[2-(2*H*-tetrazol-5-yl)ethyl]amino]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-[4-(4,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)-1-piperidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-[4-(4,5-dihydro-5-oxo-1,2,4-thiadiazol-3-yl)-1-piperidinyl]-5-quinolinyl]-cyclohexaneacetamide,

25 *N*-[6-Chloro-2-[3-(1*H*-tetrazol-5-yl)propyl]-5-quinolinyl]-cyclohexaneacetamide, trifluoroacetate,

N-[6-Chloro-2-[4-(1*H*-tetrazol-5-yl)butyl]-5-quinolinyl]-cyclohexaneacetamide,

6-Chloro-*N*-(cyclohexylmethyl)-2-[4-(1*H*-tetrazol-5-yl)butyl]-5-quinolinecarboxamide,

30 *N*-[6-Chloro-2-[(3*S*)-3-[2-(1*H*-tetrazol-5-yl)ethoxy]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-[(3*S*)-3-[2-(4,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)ethoxy]-1-pyrrolidinyl]-5-quinolinyl]-cyclohexaneacetamide,

N-[6-Chloro-2-[4-(1*H*-tetrazol-5-yl)-1-piperidinyl]-5-quinolinyl]cyclohexaneacetamide,

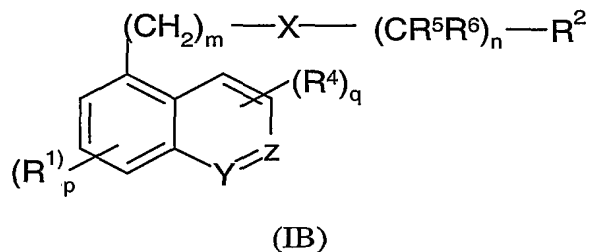
5 6-Chloro-*N*-(cyclohexylmethyl)-2-[4-(1*H*-tetrazol-5-yl)-1-piperidinyl]-5-quinolinecarboxamide,

6-Chloro-*N*-(2-cyclohexylethyl)-2-[4-(1*H*-tetrazol-5-yl)-1-piperidinyl]-5-quinolinecarboxamide,

10 6-Chloro-*N*-(cyclohexylmethyl)-2-[(3*S*)-3-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-1-pyrrolidinyl]-5-quinolinecarboxamide,

N-[6-Chloro-2-(4-cyano-1-piperidinyl)-5-quinolinyl]-cyclohexaneacetamide, or
N-[6-Chloro-2-[4-[[trifluoromethyl)sulfonyl]amino]-1-piperidinyl]-5-quinolinyl]-cyclohexaneacetamide.

15 10 . A compound of formula (IB)



or a pharmaceutically acceptable salt, prodrug or solvate thereof,

20 wherein *p* is 0, 1 or 2;

each *R*¹ is independently selected from halogen, or optionally substituted C₁₋₆ alkyl,

m is 0, 1, 2 or 3;

X is C(O)NH or NHC(O);

n is 0, 1, 2 or 3;

25 each *R*⁵ and each *R*⁶ are independently selected from hydrogen or C₁₋₃alkyl, or *R*⁵ and *R*⁶ together with the carbon atom to which they are both attached forms a C₃₋₆cycloalkyl ring, *R*² is an optionally substituted cycloalkyl group;

one of *Y* or *Z* is nitrogen and the other is a group CR³ where *R*³ is hydrogen, or a group *R*⁷, OR⁷, SR⁷, NR⁷*R*⁸, where *R*⁷ and *R*⁸ are independently selected from hydrogen, optionally

substituted C₁₋₁₀alkyl, an optionally substituted cycloalkyl or an optionally substituted heterocyclic group, or R⁷ and R⁸ together with the nitrogen to which they are attached form an optionally substituted heterocyclic ring which may contain additional heteroatoms, and may further comprise bridging groups;

5 q is 0, 1 or 2,

and each R⁴ is independently selected from halogen or optionally substituted C₁₋₆alkyl, with the proviso that where p is 0, q is 0, m is 0, n is 0, X is NHC(O), Y is nitrogen and Z is CR³ and R³ is methyl, R² is not a cyclopropyl group.

10 11. A pharmaceutical composition comprising a compound of formula (IA), or a pharmaceutically acceptable salt, prodrug or solvate thereof, as claimed in any one of claims 1 to 9 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

12. A process for the preparation of a pharmaceutical composition as claimed in claim 11
15 which comprises mixing a compound of formula (IA), or a pharmaceutically acceptable salt, prodrug or solvate thereof, as defined in any one of claims 1 to 9 with a pharmaceutically acceptable adjuvant, diluent or carrier.

13. A compound of formula (IA), or a pharmaceutically acceptable salt, prodrug or
20 solvate thereof, as claimed in any one of claims 1 to 9 for use in therapy.

14. Use of a compound of formula (IA), or a pharmaceutically acceptable salt, prodrug or solvate thereof, as claimed in any one of claims 1 to 9 in the manufacture of a medicament for use in the treatment of rheumatoid arthritis.

25

15. Use of a compound of formula (IA) or a pharmaceutically acceptable salt, prodrug or solvate thereof as claimed in any one of claims 1 to 9 in the manufacture of a medicament for use in the treatment of an obstructive airways disease.

30 16. Use according to claim 15, wherein the obstructive airways disease is asthma or chronic obstructive pulmonary disease.

17. Use of a compound of formula (IA) or a pharmaceutically acceptable salt, prodrug or solvate thereof as claimed in any one of claims 1 to 9 in the manufacture of a medicament for use in the treatment of osteoarthritis.

5 18. Use of a compound of formula (IA) or a pharmaceutically acceptable salt, prodrug or solvate thereof as claimed in any one of claims 1 to 9 in the manufacture of a medicament for use in the treatment of rheumatoid arthritis

10 19. Use of a compound of formula (IA) or a pharmaceutically acceptable salt, prodrug or solvate thereof as claimed in any one of claims 1 to 9 in the manufacture of a medicament for use in the treatment of atherosclerosis.

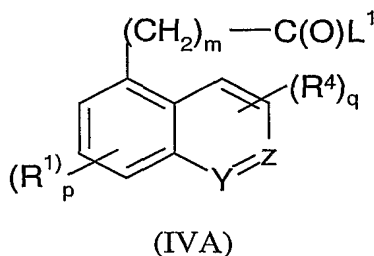
20. A method of treating rheumatoid arthritis or osteoarthritis which comprises administering to a patient a therapeutically effective amount of a compound of formula
15 (IB) or a pharmaceutically acceptable salt, prodrug or solvate thereof as claimed in any one of claims 1 to 9.

21. A method of treating an obstructive airways disease which comprises administering to a patient a therapeutically effective amount of a compound of formula (IB) or a
20 pharmaceutically acceptable salt, prodrug or solvate thereof as claimed in any one of claims 1 to 9.

22. A process for the preparation of a compound of formula (IA) as defined in claim 1, or a pharmaceutically acceptable salt, prodrug or solvate thereof, which comprises either:

25

(a) reacting a compound of formula (IVA)



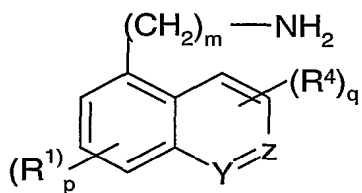
wherein L^1 represents a leaving group (e.g. hydroxyl or halogen) and Y, Z, R^1 , R^4 , m, p and q are as defined in formula (IA), with a compound of formula (VA),



(VA)

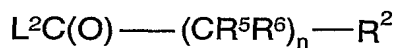
R^2 , R^5 , R^6 and n are as defined in formula (IA); or

(b) reacting a compound of formula (VIA)



(VIA)

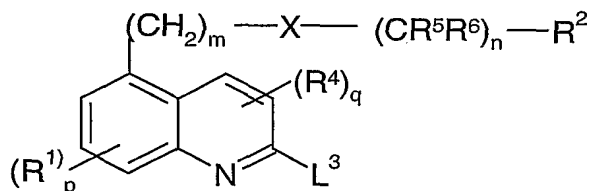
wherein Y, Z, R^1 , R^4 , m, p and q are as defined in formula (IA), with a compound of formula (VIIA)



(VIIA)

wherein L^2 represents a leaving group (e.g. hydroxyl or halogen) and R^2 , R^5 , R^6 and n are as defined in formula (IA); or

(c) when Y is N and Z is CR^3 , and R^3 represents a group of formula (IIA) above where s is 1 and X is $>NR^{11}$, reacting a compound of formula (VIII A)



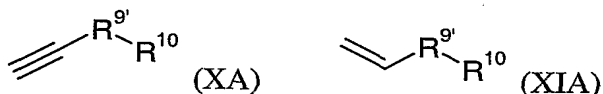
(VIII A)

wherein L^3 is a leaving group (e.g. halogen, paratoluene sulphonate or methane sulphonate), and all other variables are as defined in relation to formula (IA), with a compound of formula (IXA), $H-N(R^{11})-R^9-R^{10}$, wherein R^9 , R^{10} and R^{11} are as defined in formula (IIA); or

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(d) when Y is N and Z is CR^3 , and R^3 is a group formula (IIA) wherein s is 0 and R^9 is a C_1 - C_5 alkylene group which may be optionally substituted as defined herein above with respect to formula (IA), reacting a compound of formula (VIII A) as defined in (c) above with a compound of formula (XA) or (XIA)

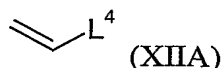
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wherein wherein $R^{9'}$ is suitably defined such that saturation of the alkene or alkyne and combination with $R^{9'}$ gives a group of formula R^9 as defined in formula (IIA), optionally followed by a hydrogenation reaction; or

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(e) when Y is N and Z is CR^3 , and R^3 is a group of formula (IIA) where s is 0, R^9 is $(CH_2)_2$ and R^{10} is $-NR^{21}R^{22}$, reacting a compound of formula (VIIA) as defined in (c) above with a compound of formula (XIIA)



20

wherein L^4 is a leaving group (eg. trialkyltin, dialkylboron or zinc), followed by reaction with a compound of formula (XIIIA), $HNR^{21}R^{22}$, wherein R^{21} and R^{22} are as defined above;

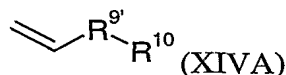
25

(f) when Y is N and Z is CR^3 , and R^3 is a group of formula (IIA) where s is 0, R^9 is (CH_2) and R^{10} is $-NR^{19}R^{20}$, reacting a compound of formula (VIII A) as defined in (c) above with a compound of formula (XIIA) as defined in (e) above, followed by an oxidation reaction and then by reaction with a compound of formula (XIIIA) as defined in (e) above under reductive amination conditions; or

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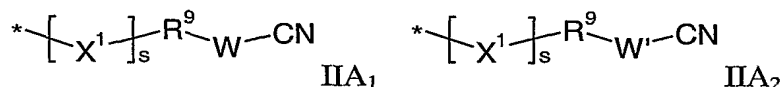
(g) when Y is N and Z is CR^3 , and R^3 is a group of formula (IIA) where s is 0, reacting a compound of formula (VIII A) as defined in (c) above with a compound of formula (XIVA)

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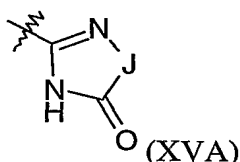
wherein $\text{R}^{9'}$ is suitably defined such that saturation of the alkene and combination with $\text{R}^{9'}$ gives a group of formula R^9 as defined in formula (IIA) and R^{10} is as defined in formula (IIA), followed by removal of any protecting groups; or

(h) when Y is N and $\text{Z} = \text{CR}^3$, and R^{23} or R^{24} represent tetrazolyl, reacting a compound of formula IIA_1 or IIA_2



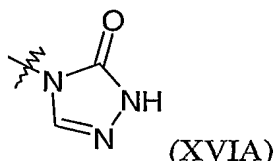
with a compound of formula PN_3 wherein P is sodium, a trialkylsilyl, an alkyltin or ammonium gives a group of formula IIA_1 or IIA_2 wherein X^1 , R^9 , W, W' are defined in IIA; or

(ii) when Y is N and $\text{Z} = \text{CR}^3$, and R^{23} or R^{24} represent a group of formula (XVA)

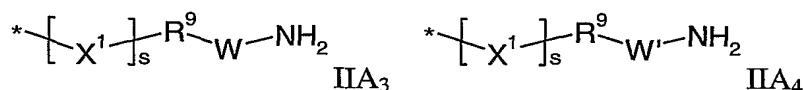


reacting a compound of formula IIA_1 or IIA_2 wherein IIA_1 or IIA_2 are as defined in (h) above with hydroxylamine, followed by treatment with 1,1'-thiocarbonyldiimidazole and subsequent treatment with silica gives a group of formula (XVA) wherein J is S, alternatively reacting a compound of formula IIA_1 or IIA_2 wherein IIA_1 or IIA_2 are as defined in (h) above with hydroxylamine, followed by treatment with a chloroformate gives a group of formula (XVA) wherein J is O; or

(l) when Y is N and $\text{Z} = \text{CR}^3$, and R^{23} or R^{24} represent a group of formula (XVIA)



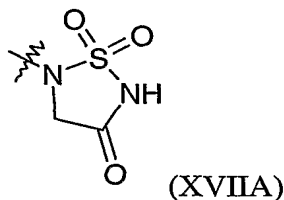
reacting a compound of formula IIA₃ or IIA₄



with a source of phosgene followed by treatment with formyl hydrazine and subsequent treatment with base; or

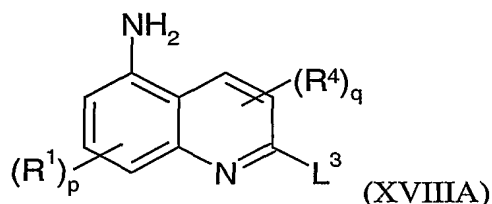
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(m) when Y is N and Z = CR³, and R²³ or R²⁴ represent a group of formula (XVIIA)



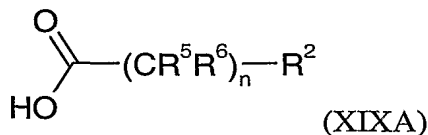
reacting a compound of formula IIA₃ or IIA₄ as defined above in (j) with ethyl
chloroacetate, followed by reaction with (chlorosulfonyl)-carbamic acid, 1,1-dimethylethyl
10 ester and subsequent treatment with acid and base gives the compound of formula
(XVIIA);

(l) when Y is N, X is NHC(O) and m is 0, compounds of the formula (VIII A) as defined
above in (c) can be derived by reacting a compound of formula (XVIII A)



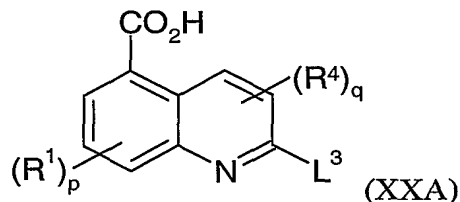
15

with a suitable acid of formula (XIX A)



20 wherein L³ is a leaving group (e.g. halogen, paratoluene sulphonate or methane
sulphonate), and all other variables are as defined in relation to formula (IA); or

(m) when Y is N, X is C(O)NH and m is 0, compounds of the formula (VIIIa) as defined above in (c) can be derived by reacting a compound of formula (XXA)

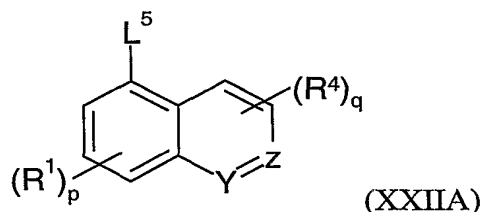


with a suitable amine of formula (XIXa)



wherein L^3 is a leaving group (e.g. halogen, paratoluene sulphonate or methane sulphonate), and all other variables are as defined in relation to formula (IA); or

10 (n) when Y is N, X is C(O)NH and m is 0, compounds of the formula (VIIIa) as defined above in (c) can be derived by reacting a compound of formula (XXIIa)



15 with a suitable amine of formula (XXIA), wherein L^5 is a halogen (e.g. bromine or iodine) and all other variables are as defined in relation to formula (IA) with a suitable source of carbon monoxide and a suitable catalyst;

and optionally after (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l), (m) or (n) carrying out one or more of the following:

- converting the compound obtained to a further compound of the invention
- 20 • forming a pharmaceutically acceptable salt, prodrug or solvate of the compound.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 2004/000836

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 215/38, C07D 217/22, A61K 31/47, A61P 37/00, A61P 11/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI DATA, CHEM. ABS DATA, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	WO 03080579 A1 (ASTRAZENECA AB), 2 October 2003 (02.10.2003) --	1-22
X	STN International, fileCHEMCATS, Accession no. 11 January 2001, Cyclopropanecarboxamide, N-(2,6-dimethyl-5-quinoliny1)- (9CI) (CA INDEX NAME), CAS Registry No. 313479-89-9 --	10
A	STN International, file CHEMCATS, Accession no. 2002:1977776, 9 July 2002, BAS 1098675, Cyclopropanecarboxamide, N-(2-methyl-5- quinoliny1)-, CAS Registry No. 333432-34-1 --	10

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

15 Sept 2004

Date of mailing of the international search report

17 -09- 2004

Name and mailing address of the ISA/

Swedish Patent Office

Box 5055, S-102 42 STOCKHOLM

Facsimile No. +46 8 666 02 86

Authorized officer

Carolina Gómez Lagerlöf/Eö

Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 2004/000836

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>US 20010003121 A1 (ANDREW BAXTER ET AL), 7 June 2001 (07.06.2001)</p> <p style="text-align: center;">-- -----</p>	1-22

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 2004/000836

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **20-21**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2004/000836

Claims 20-21 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

31/07/2004

International application No.

PCT/SE 2004/000836

WO	03080579	A1	02/10/2003	EP	1399103	A	24/03/2004
				SE	0200920	D	00/00/0000
				US	20040134103	A	15/07/2004

US	20010003121	A1	07/06/2001	US	6303659	B	16/10/2001
				AT	224360	T	15/10/2002
				AU	744280	B	21/02/2002
				AU	1791399	A	28/06/1999
				BR	9813390	A	03/10/2000
				CA	2312420	A	17/06/1999
				CN	1284057	T	14/02/2001
				DE	69808130	D,T	28/05/2003
				DK	1036059	T	02/12/2002
				EE	200000378	A	17/12/2001
				EP	1036059	A,B	20/09/2000
				SE	1036059	T3	
				ES	2184352	T	01/04/2003
				HU	0004434	A	28/05/2001
				ID	28003	A	00/00/0000
				IL	136369	D	00/00/0000
				JP	2001525392	T	11/12/2001
				NO	20002786	A	31/07/2000
				NZ	504447	A	26/04/2002
				PL	340906	A	12/03/2001
				PT	1036059	T	28/02/2003
				RU	2214997	C	27/10/2003
				SE	9704544	D	00/00/0000
				SI	1036059	T	00/00/0000
				SK	8432000	A	11/12/2000
				TR	200001605	T	00/00/0000
				US	6201024	B	13/03/2001
				US	6258838	B	10/07/2001
				WO	9929661	A	17/06/1999
